Do Variations in Treatment of Ductal Carcinoma in Situ Affect Outcomes?

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Curriculum Vitae

Heather Taffet Gold was born in Los Angeles, California on May 27, 1970. She attended the University of California at San Diego from 1988 to 1992 and graduated with a Bachelor of Science degree in Biology in 1992. She then attended the University of Chicago from 1992 to 1994 and graduated with a Master of Arts degree in public policy studies in 1994. Ms. Gold came to the University of Rochester in the fall of 1998 and began graduate studies in health services research and policy. She received a National Research Service Award Trainee Fellowship in 1998 and 1999 and a Health Care Financing Administration Dissertation Fellowship in 2001. She pursued her research in health services research and policy under the direction of Professor Jack Zwanziger and with the guidance of her committee members, Professors Andrew Dick, Charles Phelps, and Jennifer Griggs.

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Abstract

Ductal carcinoma in situ (DCIS) is a noninvasive form of breast cancer with a distinct disease pathology and natural history compared to invasive breast cancer. Its incidence has increased since the widespread use of screening mammography. Earlier detection of the disease and changing treatment patterns for early invasive breast cancer have led to treatment changes for DCIS without an understanding of the natural history of DCIS. The lack of information on the natural history of DCIS has led to doubts about the best way to treat it and has given rise to substantial variations in treatment patterns for the disease.

The overall objective of this project is to examine the effects of geographic and temporal variation in the treatment of women diagnosed with unilateral DCIS. The study will test two major hypotheses: (1) there is statistically significant geographic and temporal variation in the treatment of women with DCIS, both in type of surgery (mastectomy or breast-conserving surgery) and use of radiotherapy; and (2) variation in treatment of DCIS has consequences for rates of recurrence of DCIS and development of subsequent invasive breast cancer.

This research is based on data from the Surveillance, Epidemiology and End Results (SEER) program linked with Medicare claims data from 1991-1998, the Dartmouth Atlas of Health Care in the United States, and US Census data. The longitudinal, observational study uses econometric methods to advance the field of measuring geographic variation and to analyze the impact of treatment choice, region

effects, and socioeconomic factors on patient outcomes for women ages 65 and older.

Geographic location and year of diagnosis are significant predictors of treatment choice for DCIS, indicating geographic and temporal variation in treatment patterns. The results of the outcomes analysis strongly suggest that treatment of DCIS with mastectomy or breast-conserving surgery (BCS) with radiotherapy are much better than with BCS alone. Disease-free survival 6 years after diagnosis and treatment by mastectomy or BCS with radiotherapy is 96% compared to 86% for BCS alone. Treatment with mastectomy or BCS with radiotherapy produces superior outcomes compared to BCS alone which is the worst in terms of disease-free survival.

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Chapter 1

Background

Introduction

Ductal carcinoma in situ (DCIS) is a noninvasive form of breast cancer with a distinct disease pathology and natural history compared to invasive breast cancer. DCIS typically presents as asymptomatic calcifications of less than 10 mm on mammography, and the presumably malignant cells remain at the site of origin in the ducts (1,2). Unlike invasive breast cancer, DCIS is not associated with the risk of metastatic disease. DCIS, by definition, does not invade the basement membrane or metastasize. The disease can develop into a local invasive recurrence in the breast, however, that could lead to breast cancer metastasis and mortality (3). Approximately 50% of local recurrences following DCIS diagnosis and treatment are invasive (1), but the 10-year risk of breast cancer death is low at under 2% (4).

The treatment options for DCIS are similar to those for early breast cancer: mastectomy or breast-conserving surgery (BCS) with or without radiotherapy and more recently, with or without the addition of hormonal therapy such as tamoxifen. The controversies over treatment for DCIS exist because it is unclear which women might do better after a total mastectomy or might benefit from radiotherapy in addition to BCS. DCIS is interesting to study because of the downstream mortality risks associated with a subsequent breast event – that is, a recurrence of DCIS or development of invasive breast cancer – and the increasing incidence of the disease (1), as well as the quality-of-life trade-offs associated with the different treatment

options. In addition to any clinical uncertainty about treatment, the treatment choice involves the difficult decisions of breast preservation and undergoing weeks of radiation treatment.

This dissertation addresses several key aspects of the uncertainty surrounding best treatment for DCIS. The first analytic component identifies factors affecting initial treatment choice and geographic variation in treatment. The second element links treatment choice to the probability of subsequent breast events. Before delving into the methodological components, this background section describes the literature about the changing incidence and treatment of DCIS, its links to treatment for early invasive breast cancer, and how geographic variations play a role in treatments chosen. The second chapter discusses in detail the data and methods used, along with the measurement issues raised when pursuing a study of this kind. This is followed by the third chapter which outlines the results of the analyses. Finally, the last chapter provides a discussion of the results, including the implications this study has for care of women diagnosed with DCIS and the limitations of the data and methods.

Background and Significance

The incidence of DCIS has increased substantially since the advent of the widespread use of mammography in the early- to mid-1980s (5). From 1973 to 1983, the average annual increase in age-adjusted incidence rates of DCIS was only 3.9%, compared to a 17.5% average annual increase from 1983 to 1992. This corresponds to an overall increase in age-adjusted incidence of 557% from 1973 to

1992 (5). This increase in incidence is higher than for any other type of breast cancer (2). DCIS was estimated to account for approximately 18% of all new breast cancer cases in 1999, or almost 19,000 new cases in women ages 60 and over (6).

The risk factors for DCIS appear to be similar to those for invasive breast cancer. In particular, a family history of breast cancer, delayed childbearing, nulliparity, and increasing age are associated with a higher risk for both DCIS and invasive breast cancer for women ages 50 and older (7). This suggests that DCIS and invasive breast cancer may have similar origins although it does not prove that DCIS is a precursor to invasive breast cancer.

Accompanying the increased incidence of DCIS is an increase in the heterogeneity of the disease. Unlike mammographically-detected disease which generally is smaller and asymptomatic, cases diagnosed prior to the widespread use of mammography usually were palpable and frequently presented with nipple discharge (2,3,8). In addition to the different clinical presentations of the disease, DCIS also is microscopically diverse (2,9).

A proportion of DCIS tumors will progress to invasive breast cancer if left untreated, and some may recur after treatment (2,9,10). Autopsy studies show, however, that latent DCIS may be present and never progress to invasive disease (1,2,11). Estimates of the prevalence of DCIS at autopsy ranged from 0% to 14.7% (median, 8.9%) in women not known to have had breast cancer in their lifetime (11). New DCIS cases are not all indolent, however. The proportion of high-grade, quickly-growing lesions has also increased over time (8).

The risk of mortality from DCIS has always been small. Only 1.9% of women diagnosed with DCIS between 1984 and 1989 died of invasive breast cancer after 10 years of followup (4). This percentage is lower than the cohort of women diagnosed in the 5-year period prior to 1984, which could be due to better diagnostic tools, earlier diagnosis, or improved treatment strategies.

The disagreement and uncertainty over the best treatment for the disease arises from the heterogeneity of DCIS, the risk of subsequent breast events associated with BCS, and the differences across and limitations of treatment studies (3,5,8). The use of either mastectomy or BCS with or without radiotherapy is effective in treating DCIS (3,10,12-15), but there is no consensus on the most appropriate treatment. The only randomized controlled treatment trials have compared BCS with or without radiotherapy (12,15,16). A recent meta-analysis suggests that BCS should be followed by radiation for DCIS patients with certain risk factors, including high-grade lesions, necrosis, and close surgical margins. Patients without these risk factors, however, may be good candidates for BCS alone. For risk-averse patients, mastectomy appears to be optimal because it yields the lowest recurrence rate (10).

Overdiagnosis and overtreatment are potential problems faced by women with DCIS, because many cases of DCIS may never progress to invasive breast cancer. Women who might not benefit from extensive surgery but receive mastectomy may suffer the consequences unnecessarily. More extensive surgery, such as mastectomy, may reduce quality of life compared to BCS at least in the short

term due to diminished cosmetic results and function (17-20), but this has only been studied in patients with invasive breast cancer, not DCIS.

Influences on the Increased Use of Breast-Conserving Surgery for Early Breast Cancer and DCIS

As treatment has shifted towards less-extensive surgery for early invasive breast cancer, so has it changed for DCIS. Physicians have been recommending BCS over mastectomy for DCIS based on clinical trials of invasive breast cancer treatment.

The Halsted radical mastectomy was the standard of care until the 1960s when the modified radical mastectomy was proven to yield the same survival benefits as the radical mastectomy in treating invasive breast cancer (21,22). The modified radical mastectomy slowly gave way to even less-extensive surgical techniques, such as partial and simple mastectomy and BCS, often followed by radiotherapy for local control of the disease. These treatments yielded reduced morbidity and even less disfigurement because only a limited amount of tissue was removed. In the mid- to late-1970s, these less radical, breast-conserving surgeries were shown to have survival rates similar to the modified radical mastectomy (23-25).

The extrapolation of treatment trial results for invasive breast cancer to DCIS can be considered diffusion of a treatment strategy across distinct diseases. This trend towards use of less-extensive surgery for DCIS may have been linked to social

and political activities that affected treatment for invasive breast cancer. The Women's Movement and Women's Health Movement of the 1960s and 1970s empowered women to be active health care consumers such that they could insist on receiving certain services (26). Women demanded breast-conserving surgery over mastectomy for breast cancer. Even if not proven appropriate or adequate, women diagnosed with DCIS in the 1980s and 1990s may have pushed for the quick uptake of BCS for DCIS. And with this trend, some physicians elected or suggested not to give radiotherapy after BCS particularly if the surgery yielded clear margins (no cancerous cells close to the edge of excision). This diffusion has led to variations in treatment across geographic areas and over time.

Geographic and Temporal Variations in Treatment of Invasive Breast Cancer and DCIS

The clinical, social, and political activity surrounding breast cancer treatment has led to variability in treatment patterns across the United States. Since 1983, geographic and temporal variations in the treatment of early invasive breast cancer have been demonstrated by multiple investigators (23,25,27-31). For example, one study showed substantial geographical variation in the use of BCS in SEER regions, with a range of 9% in Iowa to 32% in Seattle in 1983 followed by a steady increase in the use of BCS in all states studied over the years 1983 through 1986 (29). Among Medicare beneficiaries ages 65-79 diagnosed with local or regional breast cancer in 1986, 3.5% in Kentucky received BCS, whereas 21% in Massachusetts did (30).

Analysis of the American College of Surgeons' voluntary National Cancer Data Base (NCDB) also showed uneven rates of the use of BCS across states, from 7% in Mississippi to 64% in Massachusetts in 1991 (32). Finally, in a medical record abstraction study of two states from 1993 to 1995, Massachusetts showed 74% of women undergoing BCS for early-stage breast cancer when clinically appropriate, whereas Minnesota's rate was lower at 48% (33). Even when different data sources are examined, from Medicare claims to the National Cancer Data Base, clear geographic variation is seen in the rates of BCS for the treatment of early invasive breast cancer.

Variations in treatment for early invasive breast cancer may be affected by nonclinical characteristics, including rural or urban region, age, race, income, year of diagnosis, hospital size, surgeon volume, and patients' preferences. Older age, for example, is associated with a lower likelihood of receiving BCS followed by radiation therapy compared to mastectomy (25,29,32,34), even after adjusting for comorbidity and stage of disease (35,36). Researchers have found that after adjusting for many socioeconomic factors and stage of disease, lower income and education and a higher poverty rate within the patient's zip-code area predicted the lower use of BCS among Medicare beneficiaries (37). Others showed that higher patient income and prevalence of radiation oncologists increased the probability a woman received BCS, whereas rural residence and a higher poverty rate in a region reduced the likelihood (32). Women receiving care in hospitals with over 500 beds or from surgeons with a higher caseload of breast cancer patients (greater than 50

cases from 1985 to 1987) were more likely to receive partial mastectomy and radiation rather than modified radical mastectomy in the metropolitan Detroit area. The probability of undergoing partial mastectomy with radiotherapy increased over time for black women, but decreased for white women as BCS became more widely-used for the white population during this time period (34). Finally, the patient's decision and deliberation over treatment choice, including a woman's risk aversion and fear of recurrence (38), play a role in what treatment she receives (39,40).

The increasing use of less-extensive surgery for invasive breast cancer has led to treatment changes for DCIS (12,13,41), even though there are few direct studies of DCIS treatment strategies and no randomized controlled trials of mastectomy versus BCS for DCIS (3). Between 1983 and 1992, the total percentage of DCIS cases treated by BCS increased from 25.6% to 53.5% according to analysis of the SEER data (5). In 1992, the use of BCS for DCIS varied across SEER regions and ranged from 28.8% in Connecticut to 57.7% in New Mexico (5). The NCDB shows a similar pattern of increased use of BCS for DCIS, from 31% in 1985 to 54% in 1993, with a concurrent increase in adjuvant radiotherapy use from 38% to 54% (42). Underlying the shift towards less-invasive surgery for DCIS is the assumption that the benefits of mastectomy might not outweigh its consequences for DCIS, but there still is uncertainty about the optimal treatment.

Other factors may be related to DCIS treatment patterns in the NCDB hospitals, but multivariate analysis has not shown their statistical significance. Geographic region of patients with DCIS may be important in determining which

treatment they receive, as those in the Northeast were much more likely to receive BCS (60%) compared to those in the South (39%) from 1990 to 1993 (42). Black and white women were less likely to receive radiotherapy following BCS compared to Asian-American and Hispanic-American women (42).

Theories of Geographic Variation in Use of Clinical Services

Geographic variation in treatment for DCIS and early invasive breast cancer is not unexpected. Geographic variations have been found to exist across countries and regions for many health conditions, hospital admission rates, mortality rates, lengths-of-stay, and surgical, diagnostic testing, and medical rates (16,43-55).

Many factors lead to the early or late use of a new innovation such as a new surgery style. Early work on diffusion of technology showed that diffusion assumes an S-shaped curve, and this finding held for fields as diverse as agriculture (56,57). Technologies are more easily and likely to be adopted if they are similar to current values and activities and have at least some benefit for their potential adopters (58,59). In the case of breast cancer, it might be difficult for some physicians to embrace a new, less-extensive type of surgery, BCS, because without performing a mastectomy, it might seem that the physician did not use all means to help the patient. Moreover, if BCS were reimbursed with a lower total payment than mastectomy, the incentive to perform mastectomy is even greater. Phelps suggests that in the diffusion of health care technology, the inferior strategy is not necessarily

abandoned altogether, however, and that "there seems to be no convergence through time in the use of specific interventions" (60).

Four distinct patterns of variations have been shown in the literature (61). These are 1) consistency in procedure-specific variation regardless of the procedure being studied (e.g., hysterectomy has greater variation in use than appendectomy regardless of geographic area), 2) procedure consistency over time whereby high users remain high and low users remain low, 3) high-use or low-use areas have consistently high or low use across several measures, and 4) variation in treatment for medical diagnoses is consistently greater than variation in surgical procedures (61). The broad array of variations studies shows that variation is lower when the disease is easier to diagnose, the treatment is fairly clear-cut, and there are known adverse effects of not treating (60). Variations tend to increase when there are treatment alternatives and some uncertainty about those alternatives (60). DCIS fits the criteria for high variability in treatment.

Many explanations have been proffered for the wide variation in practice patterns, several of which will be explored here. The first explanation is that medical uncertainty or differing beliefs about efficacy may lead to physicians using the intervention they believe is optimal. The chosen strategy will vary across communities and regions (60,62-64), because "individual physicians tend to follow what is considered standard and accepted in the community" (65). This is a reasonable explanation when there are few or no clinical trials comparing treatment modalities. A study of variation in the use of certain surgical procedures shows that

across New England, the West Midlands of the United Kingdom, and Norway, procedures with lesser consensus about their use have higher variability, supporting the theory that uncertainty may play a role in variation (66). When there is adequate information about optimal treatment strategies, such as from an NIH Consensus Development Conference or randomized clinical trial, however, the diffusion of information still may be uneven and slow due to high costs of acquiring the information or of changing practice patterns (60,62).

Clearly there is uncertainty about the optimal treatment strategy for DCIS. This likely is due to the lack of clinical trials comparing BCS to mastectomy. There are trials comparing BCS to BCS with radiotherapy that provide some information to aid the treatment decision (12,15), but this does not address all possible treatment options for DCIS nor differences in outcomes.

Another possible explanation for geographic variation is that inappropriate use may be occurring in regions with high rates of procedures due to supply-side factors such as induced demand or availability of resources (62,65,67). Wennberg shows that a population's medical admissions rate is highly correlated with the number of hospital beds per capita, especially for "high-variation" conditions – those with several treatment options and uncertainty about whether hospital admission is necessary (e.g., chest pain) (64). Variation is not due solely to physician-induced demand, whereby physicians know there are beds available to use and know they would be remunerated for using the beds, because similar correlations exist in countries such as Great Britain where different economic incentives hold (62).

Research has shown that inappropriate use or overuse of three procedures (carotid endarterectomy, upper gastrointestinal endoscopy, and coronary angiography) occurred in regions with high and low use rates. Physicians in high-rate counties were not conducting inappropriate procedures more often (51). Others demonstrated that variation in the use of certain surgical procedures persists across three countries, suggesting that the organization and financing of health care does not explain variation for the procedures studied (66).

Inappropriate use of treatment type may be occurring because of incentives surgeons and radiation oncologists have in treating DCIS. Since no one really knows what use is appropriate, it is hard to measure what might be induced. If surgeons receive higher remuneration for certain types of procedures, they might be more eager to do the more highly-reimbursed procedures if such procedures take relatively less time. If surgeons believe that their patients will not be able to comply with radiation appointments after surgery, the physicians might perform a more extensive surgical procedure so the patient does not have to return.

The third theory to explain geographic variation is that underlying patterns of illness and population characteristics could affect use rates. For example, if one region tends to have sicker patients that need more extensive therapy, the rates of use of that intervention will appear higher in the sicker region. Wennberg argues that geographic variations in hospitalization rates are not well correlated with age, gender, socioeconomic factors, or morbidity differences (64), and little of the variation is explained by differences in underlying illness rates or morbidities (16).

Others demonstrate, however, that socioeconomic status independently explains 19% of the variance in surgical admissions and 48% for medical admissions across areas in Michigan (68) but it is unclear if these are necessary or inappropriate admissions. If multivariate analysis cannot account for underlying population differences, then some residual variation could still be due to disease prevalence differences and population characteristics.

Certain population characteristics could explain some of the variation in the use of BCS. For breast cancer, BCS has been used more often in women of higher income and education (37), who live in urban areas (69) or are in closer proximity to radiation-treatment facilities (70,71), and who are of younger age among women ages 65 and older (35). Zip-code areas with larger African-American populations were found to have greater use of mastectomy, but this could have been due to disease being found at later stages rather than due to race, because one study incorporating this variable did not control for disease stage (72) or for health insurance status, both of which can affect timeliness of screening (73).

Women with smaller and lower-grade DCIS tend to undergo BCS rather mastectomy (42), but if these characteristics are uncorrelated with region, then this association will not help explain geographic variation. Without controlling for particular characteristics of the tumor, one could miss the underlying explanation or justification for the treatment.

Another possible reason for geographic differences in treatment rates is random variation (60,74). Because so many factors have been shown to explain

much of geographic variation (e.g., socioeconomic variables, age, gender), however, it is unlikely that random noise explains all of the disparity across regions (62). In addition, several researchers have proven through statistical tests that the differences in procedure rates due to geographic variation are much greater than chance, or random variation, alone (55,58,75)

Some might argue that physician enthusiasm for particular services, rather than uncertainty, creates geographic disparity in use rates (76). Data show that both a higher prevalence of surgeons and a higher percentage of those surgeons performing carotid endarterectomy in a high-use region leads to a higher prevalence of surgeons performing the procedure overall in that region. Also, as practice volume increases in the high-use areas, so does the number of surgeons per capita. This may be because a larger number of surgeons in one area who are "enthusiastic about a procedure" causes geographic differences in use rates (76). This hypothesis may coincide in some ways with the uncertainty hypothesis, because enthusiasts may believe in something about which they have misinformation or for which there is little scientific data. They may not recognize outright that the scientific basis for a procedure is minimal for some of their patient population but based on their experience they perform a particular procedure regardless.

It is possible that physicians in a certain region are enthusiastic and supportive of the use of BCS for DCIS, which would help explain the variation in the use of BCS. Perhaps they are trend-setters in surgical techniques for invasive breast cancer, and they believe that many women with DCIS will not benefit from

mastectomy. And, if they think they can obtain clear margins, they might conduct BCS alone without providing a radiotherapy referral.

Others theorize that defensive medicine or the malpractice environment may also create variation in care (32,65) because until recently, the malpractice standard typically was the community norm rather than national, scientifically-based criteria (60). This puts pressure on physicians to behave similarly to their local colleagues.

Because there is uncertainty about the best way to treat DCIS, defensive medicine or malpractice concerns could affect the way surgeons operate. This argument holds for a study of physicians who treat women with invasive breast cancer (77). Also, if many physicians in a region are performing BCS on women with DCIS, it may become the community norm with resultant pressure to conform to these standards.

There may also be a simple substitution in production such that physicians choose to use one procedure over another because of the net revenue differences, the ease of use of one technique or procedure, or familiarity of a particular procedure (78). Being comfortable with performing mastectomy rather than BCS for DCIS, for example, would lead some physicians to continue in that way so they do not have to learn a new technique particularly when their colleagues may not be adopting new treatment practices.

Finally, specific policies or laws may affect geographic variation in use of procedures (79). If one state has a law that encourages certain types of behavior, such as informed consent or participatory medical decision-making for treatment,

then that state may end up with different levels of use of particular interventions because patients become knowledgeable about their options.

State informed consent laws for breast cancer treatment may affect which treatments are performed on women diagnosed with DCIS. Just having the information that there are treatment choices – BCS, BCS with radiotherapy, or mastectomy – could influence decisions physicians and patients make. There is only mixed evidence, however, that the state laws on breast cancer informed consent have had an impact on surgeons' practices (79,80).

The trend towards the use of BCS for DCIS and early breast cancer may have been caused by any of the above reasons – from innovative physicians to environments promoting adoption of BCS. As with other clinical interventions, the theories supporting geographic variation may hold for the use of particular treatments for DCIS.

Current treatments for DCIS are suboptimal if not all of the geographic variation is explained by differences in patient preferences and clinical presentation and if variation adversely affects health outcomes. If decisions about treatment are being made based on local norms, random variation, or physician preferences or incentives, then women are not necessarily receiving care in their best interests and there is welfare loss in society.

Effect of Geography on DCIS Treatment and Subsequent Breast Events

Geographic variations are studied often but are not always linked to an analysis of health outcomes. This is a limitation of much research but is an area which this dissertation addresses in order to improve the management of DCIS for older women. Several articles have assessed the link between variations and outcomes, however, including mortality associated with hospital utilization differences (47) and geographic variation in use of radical prostatectomy (46).

A study linking geographic variation to outcomes addressed the use of radical prostatectomy for prostate cancer (46). The findings indicated that the use of radical prostatectomy increased over time, the range of rate differences across regions grew larger over time, and there were no significant variations over time or across regions in the outcomes of mortality or morbidity even with the rate differences. The study suggests that prostatectomy may not improve outcomes, because outcomes were the same even with different regions performing the procedure at different rates (46).

As mentioned previously, research on DCIS treatment is insufficient, and there is only one known study of geographic variation in treatment patterns which used the geographic region as the unit of analysis, rather than the individual. The authors did not show if geographic region or individual-level variables had an impact on patient outcomes, however (5). The present study provides a helpful synthesis of the effects of treatment socioeconomic and geographic factors on rates of subsequent breast events. Outcomes to be assessed include recurrence of DCIS and subsequent invasive breast cancer.

Summary

Using data from the Surveillance, Epidemiology, and End Results (SEER) program linked to Medicare claims, this study will analyze variations in treatment patterns for DCIS and will assess differences in health outcomes due to three treatments for DCIS: BCS alone, BCS with radiotherapy, and mastectomy. In the outcomes element of the study, several methodological issues arise, including the most important one: what does one do about the unmeasured or unobservable factors that might affect treatment choice and/or outcomes but which are not incorporated into the model? Because secondary data sources, such as the linked SEER-Medicare database, provide limited information about health status and extent of disease, econometric methods must be used to estimate if this unobserved information is important and, if so, what can one say about the impact of those unobserved variables on outcomes.

The second chapter of this dissertation outlines the data being used and discusses the econometric methods and technical issues raised by a study such as this. The third chapter provides results, and the last chapter discusses the results, conclusions, and their implications for clinical policy.

Chapter 2

Data and Methods

Data

The primary data source for this study is the Surveillance, Epidemiology, and End Results program (SEER) data linked with Medicare claims for cases of ductal carcinoma in situ (DCIS) diagnosed from 1986-1996 (with claims through 1998). The SEER registry data are population-based but are not a random sample of the population of the United States. The 11 SEER registries represent 11-14% of the US population.[1] The data contain month and year of diagnosis, basic histology codes and site of diagnosis, therapy administered within 4 months of diagnosis, and patient demographics. For persons diagnosed with cancer at age 65 or older and reported to SEER registries, 93% of them could be linked to the inpatient, outpatient, and physician Medicare administrative files (81).

Women selected for inclusion in the analytical sample are those ages 65 and over with a first diagnosis of DCIS (behavior code 2, histology code 8500, and SEER tumor sequence number 00 or 01), yielding 4,611 cases after exclusions (see Table 2-1). The sample does not include women who had a prior primary diagnosis of cancer. Patients then included for analysis of all three treatments are women diagnosed from 1991 to 1996 who were treated at minimum with breast surgery. Excluded from the outcomes analysis are women who were in a health maintenance

[1] The SEER program is considered the authority and standard for quality in determining cancer incidence, mortality, and survival statistics for the United States (119). Complete years of data are available for all registries except the Los Angeles and San Jose, California, registries which joined SEER in 1992.

organization (HMO) during the month of diagnosis and for the next 2 years (n=580), because Medicare claims are not available to determine treatment or possible subsequent breast event during that time, and this 2-year period captures most women who were in an HMO during followup.[2] The month and year of diagnosis of DCIS are from the SEER data, with the assumption that the diagnosis was made on the first of the month of diagnosis, because the exact day of diagnosis is unavailable. To obtain first cases of unilateral DCIS, I also excluded cases in which the date of diagnosis of first DCIS is the same as the month and year of diagnosis for a second primary breast-related tumor based on SEER data (cancer site recode 46). The final sample included 2,701 women for the analysis of geographic variation from 1991-1996 (no exclusions for being an HMO member after diagnosis because only initial treatment is of interest) and 2,192 for the analysis of outcomes across all three treatment regimens.

The Medicare surgical claims are the "gold standard" to identify the extent of surgery for the initial diagnosis of DCIS. Others have shown this to be a valid method of identifying breast cancer surgery type (82,83). In a study using the SEER-Medicare data from 1991 through 1993, agreement across databases was shown. Among patients with surgery information within 4 months of diagnosis from Medicare and SEER, 95% of patients receiving mastectomies according to Medicare claims were confirmed by SEER, and 91% of BCS cases were corroborated (83).

[2] Excluding women who were ever in an HMO yields virtually identical results. Women who enroll in an HMO beyond 2 years after diagnosis are censored at that point.

Table 2-1. Data and Exclusions for Initial Sample of Cases and for Analytic Samples of Linked SEER-Medicare Data, 1986-1998.

	n	Data source
DCIS cases abstracted	**8453**	SEER-Medicare
Exclusions (as subsequent steps, so no overlap of cases):		
1) Diagnosis prior to 1986	267	SEER
2) Case found at autopsy	4	SEER
3) Patient younger than age 65 at first diagnosis	2936	SEER
4) Medicare eligibility due to ESRD*	30	SEER
5) Unknown month of first diagnosis	5	SEER
6) Unknown month of second diagnosis	1	SEER
7) No surgery information	544	SEER-Medicare
8) Breast cancer or DCIS diagnosis concurrent with first primary DCIS diagnosis	55	SEER
Subtotal	**4611**	
Geographic Variations Analysis, three treatments, 1991-1996		
1) Diagnosis prior to 1991	1797	SEER-Medicare
2) Missing Census data	57	1990 Census data
3) Missing radiation oncologist data	56	Dartmouth Atlas
TOTAL	**2701**	
Outcomes Analysis, three treatments, 1991-1998		
1) Diagnosis prior to 1991	1797	SEER-Medicare
2) In HMO at month of diagnosis or during 24 months after diagnosis	622	SEER-Medicare
TOTAL	**2192**	

*ESRD refers to end-stage renal disease, a condition that creates automatic eligibility for Medicare benefits.

Medicare claims for radiotherapy are combined with SEER designation of radiotherapy, as suggested by previous work (84). There is a risk of disagreement between the data sets if only 1 source is used for ascertaining radiotherapy status. In a 1999 study of breast cancer patients, it was found that 7.4% of cases identified as undergoing radiation according to SEER were not identified as such in Medicare claims (84). By combining information, one hopes to have a more accurate representation of which patients are undergoing radiotherapy.

In this study, surgery claims were searched from two months (66 days) prior to the date of diagnosis of DCIS up to and including 6 months (183 days) post-diagnosis to obtain the most-extensive surgical claim associated with a breast-cancer diagnosis during that time.[3] (See Table 2-2 for a list of codes.) The two surgery types include breast-conserving surgery (also known as lumpectomy) and mastectomy. If excision or biopsy were accompanied by radiation therapy, the initial surgery type was defined as breast-conserving surgery, because in general a biopsy is diagnostic, but radiation therapy indicates directed treatment for breast cancer or DCIS. If no surgery information were found in Medicare claims, then the SEER surgical code was used, which indicates the type of surgical treatment within 4 months of diagnosis. The cases without Medicare surgical information include 149 for the 1991-1996 outcomes analysis, 468 for the 1991-1996 geographic variations analysis (higher due to HMO status during month of diagnosis), and 154 for the mastectomy-only study from 1986-1996. Incorporating SEER surgical information is justified

[3] Six months for the initial treatment period was chosen because most women should have directed treatment within this time.

because the concordance between surgical type in Medicare and SEER was quite high for all cases from 1991-1996, when inpatient, outpatient, and physician claims are available and overlap. The percentage agreement or total cases that agree overall is 86.5%. Of those with mastectomy according to Medicare claims, 91.1% were confirmed by SEER, and of those with BCS according to Medicare claims, 96.6% were confirmed by SEER. Of those without surgery according to SEER, 88.1% were confirmed by Medicare as not having surgery.

Women were designated as undergoing radiation treatment if there were two or more Medicare claims for such treatment. Other studies have allowed for just one claim to indicate that radiotherapy was performed (84) but requiring two or more claims makes it more likely that the claims data are not recording a false-positive treatment or single visit without a full course of treatment. (Including 1 or more radiation visits would increase the number receiving radiotherapy by 12.) Because 1991 is the first year that outpatient and physician claims are available to indicate whether a woman had radiotherapy or not, for comparison of all three treatment regimens, only 1991-1996 data are used. As done with defining initial surgery type, if Medicare claims were not found to indicate an initial course of radiotherapy but the SEER data indicated such treatment (within 4 months of diagnosis only), then the patient was considered to have undergone radiation treatment.

Concordance rates of radiotherapy data across Medicare and SEER were lower than surgery data. Of those with Medicare claims indicating radiation treatment, 90.8% were confirmed by SEER. However, of those with SEER

designation of radiotherapy, only 79% were confirmed by Medicare. These data sources complement each other, but do not overlap completely (84).

A priori I assumed that mortality rates for women diagnosed with DCIS were similar to all-cause female mortality rates, and this was confirmed by comparing the empirical age-specific overall mortality rates of women diagnosed with DCIS in SEER to life table estimates for females in the United States (85). The rates were virtually identical. (Data not shown.) One other study has also demonstrated the low mortality rates following DCIS diagnosis (86). Therefore, the main outcome of interest in this study is subsequent breast events, that is, recurrence of DCIS and subsequent invasive breast cancer tumors, not overall or breast cancer mortality.

Table 2-2. Medicare Claims and SEER Codes Used to Determine Initial Treatment.

Medicare diagnosis codes from all claims[a]		
ICD-9-CM	1740-1749, 2330, 1963, 19881	Diagnosis of DCIS, axillary node involvement, or breast cancer
Medicare procedure codes from NCH (Physician) & Outpatient claims[b]		
HCPCS	19120	Breast-conserving surgery
HCPCS	19160, 19162, 19180, 19182, 19200, 19220,19240	Mastectomy
HCPCS	38500, 38505, 38525, 38550, 38740, 38745	Axillary node dissection
HCPCS	77280, 77285, 77290, 77295, 77401, 77402, 77403, 77404, 77406, 77407, 77408, 77409, 77411, 77412, 77413, 77414, 77416, 77417	Radiation therapy (at least two claims)
Medicare procedure codes from MEDPAR[a]		
ICD-9-CM	8521, 8522, 8523	Breast-conserving surgery
ICD-9-CM	8541, 8542, 8543, 8544, 8545, 8546, 8547, 8548	Mastectomy
ICD-9-CM	4011, 4023, 403, 4051	Axillary node dissection
SEER treatment codes[c]		
Site Specific Surgery	10, 18, 20, 28	Breast-conserving surgery
Site Specific Surgery	30, 38, 40, 48, 50, 58, 60, 68, 70, 78	Mastectomy
Radiation	1, 2, 3, 4, 5, 6	Radiation therapy

[a] from International Classification of Diseases (87); MEDPAR indicates inpatient claims.
[b] Physicians' Current Procedural Terminology (CPT) codes (88).
[c] SEER site-specific surgery codes with an "8" in the second digit indicate reconstruction was part of the first course of therapy.

The SEER data are the source for the primary diagnosis of DCIS but SEER does not include recurrences or subsequent invasive breast cancer or metastases, only primary tumors up to the tenth. Subsequent breast events – meaning recurrence of DCIS or subsequent invasive breast cancer – therefore is defined as having a Medicare claim at minimum 183 days (6 months) after diagnosis based on the first instance of either 1) an inpatient claim with a primary or secondary diagnosis of DCIS, axillary node involvement, or breast cancer, and procedure of breast-conserving surgery (BCS), mastectomy, or axillary node dissection, or 2) an outpatient claim with a primary diagnosis of DCIS, axillary node involvement, or breast cancer, and procedure of BCS, mastectomy, or axillary node dissection, or 3) a physician-surgeon claim for BCS, mastectomy, or axillary node dissection. (See Table 2-3.) Radiotherapy occurring after 6 months from diagnosis is not included as indicating a subsequent breast event. Surgery has to be performed to be considered such. If no claims met these criteria, but a woman's cause of death was breast cancer (ICD-9-CM of 174.x), she was considered to have had a subsequent breast event at the date of death.

In some instances, claims for the same procedure but from different sources had conflicting diagnosis codes. It was therefore impossible to separate subsequent DCIS from breast cancer. For example, a physician claim might state an ICD-9-CM code of 2330 (DCIS), but the inpatient claim states 1749 (breast cancer, unspecified). Six months, or 183 days, was chosen as the first opportunity for a subsequent breast event so as not to allow any overlap of initial treatment with treatment of subsequent

breast events.[4] This search for subsequent breast events was conducted similarly to other studies that have used algorithms to search for first incident breast cancers in Medicare hospital and physician claims data (89,90).

[4] Because the decision to use 6 months is somewhat arbitrary, I altered the period to 10 months and 1 year and found no substantive differences.

Table 2-3. Medicare Claims Codes Used to Determine Subsequent Breast Events.

Diagnosis codes from all claims[a]		
ICD-9-CM	1740-1749, 2330, 1963, 19881	Diagnosis of DCIS, axillary node involvement, or breast cancer
Procedure codes from NCH (Physician) & Outpatient claims[b]		
HCPCS*	19120	Breast-conserving surgery
HCPCS*	19160, 19162, 19180, 19182, 19200, 19220,19240	Mastectomy
HCPCS*	38500, 38505, 38525, 38550, 38740, 38745	Axillary node dissection
Procedure codes from MEDPAR[a]		
ICD-9-CM	8521, 8522, 8523	Breast-conserving surgery
ICD-9-CM	8541, 8542, 8543, 8544, 8545, 8546, 8547, 8548	Mastectomy
ICD-9-CM	4011, 4023, 403, 4051	Axillary node dissection

[a] from International Classification of Diseases (87); MEDPAR indicates inpatient claims.
[b] Physicians' Current Procedural Terminology (CPT) codes (88).

Not only did I use claims data for identifying initial treatment and subsequent breast events, but for the geographic analysis I created two comorbidity indices from the data using the method described and validated by Klabunde, et al. (91). One comorbidity index is based on inpatient claims (1986-1996), and the other is based on outpatient and physician claims (1991-1996). They include claims for care for diabetes, chronic pulmonary disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, paralysis, acute myocardial infarction (inpatient only), old myocardial infarction, moderate or severe renal disease, diabetes with complications, ulcer, dementia, rheumatologic disease, and mild liver disease. The coefficients from Klabunde and colleagues, which indicate the relative impact of different clinical conditions on noncancer mortality, are applied directly to estimate the 2 individual-level comorbidity indices from claims up to a year prior to diagnosis.[5] Of women diagnosed after 1990, approximately 94% had a physician claims comorbidity index of 0, and 2 had a negative index, meaning that they had no health conditions expected to increase noncancer mortality. Almost 96% had an inpatient claims comorbidity index of 0, and less than 1% (n=17) had a negative index. For women diagnosed in 1991 in the geographic variations analysis, 360 have only an inpatient claims comorbidity index, and their physician claims index was set to 0, since that was by far the most prevalent value. The same was done for women in the mastectomy-only analysis who were diagnosed in 1986 (i.e., they have no prior-year claims).

[5] See Appendix for coefficients and see also Klabunde, Potosky, et al. (91).

In addition to claims data, I incorporated into the models demographic variables from the SEER data, including categories for age at diagnosis (ages 65-69, 70-74, 75-79, 80 and older), marital status (married or not at date of diagnosis), race (black, white, other), and registry indicators (representing 11 regions). I also used United States Census data because the SEER-Medicare data contain few socioeconomic measures, some of which could be important in determining health outcomes. Therefore, the data are supplemented with zip-code level Census data measures including educational attainment represented by the percentage without a high school education, percentage rural, and percentage living below the poverty level. (Median income was excluded due to multicollinearity.) I assign the zip-code level values as proxies to the individual cases in the sample. Rather than include the Census variables as continuous covariates, they are broken into dummy-variable categories. The percentage with less than a high school education and the percentage living below the poverty level are divided into quintile indicator variables with the highest quintiles being the least educated and in the highest poverty areas, respectively. The percentage rural is divided into 4 categories represented by indicator variables (equal to 0% rural, between 0% and 10%, greater or equal to 10% and less than 50%, and greater or equal to 50% rural).

Finally, one variable was extracted from the Dartmouth Atlas of Health Care 1999, which contains data on the health care system by hospital service area (HSA). To help explain geographic variation in use of treatment type, I obtained from the

Atlas the number of radiation oncologists per 100,000 population for each HSA, and then matched that 1993 value to the zip code of each patient.

Methods

Several methods are used to evaluate geographic variations in treatment and outcomes of care based on treatment provided. This section details the estimation procedures for geographic variation analysis and continues with a section on the methods used for the outcomes analysis. Following the description of each method, a table presents the hypothesized effects of each covariate on the outcome in question.

This study does the following: 1) quantifies the variation in treatments across region; 2) describes the change in that variation over time; 3) tests if the variation of treatment rates across regions stay the same over time or if it increases or decreases, suggesting an S-shaped diffusion process; 4) identifies if treatment patterns are related to age, region, or other covariates; and 5) describes the relationship of each treatment type with the probability of subsequent breast events and tests if the associations are different by treatment type. To answer these questions, several models must be developed, but the model parameterization raises issues of endogenous treatment choice that can affect the causal interpretation of the resulting estimates.

Geographic Variations Analysis

The analysis of treatment patterns across 11 SEER geographic regions suggests questions about the nature of the variation underlying the differences across regions and whether one can account for the variation. Three sources of variation can affect treatment rates: sampling variation, explained variation, and unexplained

variation (92). Explained variation can be eliminated by controlling for exogenous variables that affect treatment patterns. Unexplained variation across regions can be modeled using random or fixed effects for each region. Then the test of whether the random effect is zero or the fixed effects are jointly zero will identify if any unexplained variation by region remains after including the region effects (58).

One can investigate whether the amount of geographic variation in the use of certain treatments grew as the use of a technology diffused, and then declined as indications for the appropriate use of the technology became clearer. It is possible to test if the typical S-shaped diffusion process took place during the study period (59). If the diffusion of BCS (which was increasing over the study period) follows the hypothesized S-shape, the sample variance of the fixed effects will be small in the years immediately following the introduction of BCS, will increase steeply, and then will decline as the use of the technology became common or diffuse across regions.

Examination of treatment patterns across the SEER geographic regions shows to what degree, if any, practice differences exist. For the bivariate analysis, I use the chi-squared test for differences in rates of treatment use by each region, a method which is used often in the literature (45,75). Diehr and colleagues showed that the chi-squared test had the best power of detecting variation among counties in Washington State for back surgery (75). A chi-squared test of the use of treatments by geographic registries shows if there are similarities in rates of use across geographic regions by testing for equality of proportions (93-95).

This test is conducted to evaluate whether the proportions of treatments used are the same across each registry. If the proportions are not the same then the test indicates that geographic variation likely exists. In this study, the rate of use of each treatment is derived from the proportion of women receiving each treatment in the population at risk, that is, the total number of women in the sample diagnosed with DCIS. The approach uses data that are aggregated to the geographic unit in a bivariate analysis.

The SEER-Medicare data contain individual-level data about women that can be exploited to increase the number of observed factors controlled for in the model rather than aggregating to the region level. Thus, a more complex model used to estimate geographic variation in treatment practices is a multinomial logistic regression model with individual-level controls and the outcome in nominal scale (BCS, BCS with radiotherapy, or mastectomy). The multinomial logit model can be solved via maximum-likelihood estimation as discussed in Hosmer and Lemeshow and Maddala (96,97).The vector of covariates include socioeconomic variables, comorbidity indices, and fixed-effect dummy variables for each region.

To identify factors that differed by region, chi-squared (X^2) tests were calculated by treatment option for each variable or category of indicators that added to unity (e.g., quintile indicators of educational attainment). For continuous variables, two-sample t-tests were calculated across BCS and mastectomy treatments. From these statistical tests, variables with a p-value of less than 0.25 were incorporated into the model, as recommended by Hosmer and Lemeshow (96).

See Table 2-4 for hypotheses of the effects of the covariates on the probability of receiving a particular treatment.

There was multicollinearity among some of the socioeconomic variables, so the variance inflation factors (VIF) were calculated after estimating an ordinary least squares model including all potential covariates. Multicollinearity is suggested if the largest VIF is greater than 10 or if the mean of all the VIFs is considerably larger than 1. If either is the case, the variables with high VIFs can be excluded (98).

A multinomial logit model imposes the independence of irrelevant alternatives (IIA) restriction, meaning that two or more treatment categories are not associated or highly correlated or substitutes in some way. The Hausman test for IIA determines if this restriction is appropriate. The Hausman test for IIA will assess whether the coefficients change if one of the treatment options is excluded. If the coefficients do change, IIA is violated and the multinomial logit model is inappropriate (99).

Using the predictions from the multinomial logit models, one can quantify the effects of the covariates. This is done by varying the value of any covariate and predicting the probability that such a "hypothetical" woman diagnosed with DCIS would undergo each treatment strategy.

To obtain mean treatment rates I estimate the predictions using a standardized population of all women in the sample. Then I compute the mean predicted use rate of each treatment. This involves changing the region indicator variable for each person in the sample, starting with region 1, and then continuing through this process

for each region over the entire study period. The result is a mean predicted rate for each treatment for each region using exactly the same set of population characteristics across regions. Then, using the average effects by region I calculate the sample standard deviation across regions as an estimate of the variability of use of the treatment options for the entire period of the data. The sample standard deviations for each treatment can be bootstrapped to estimate a confidence interval around the statistic.

Bootstrapping the sample standard deviation allows one to assess its magnitude and to generate confidence intervals for each treatment strategy. Bootstrapping involves random resampling with replacement many times to get an estimated or simulated confidence interval to represent the underlying distribution of the test statistic, the sample standard deviation (100).

By comparing the bootstrapped sample standard deviations for each treatment based on models with and without covariates, it is also possible to identify if the standard error changes after controlling for covariates. If it is smaller, then the geographic variation in treatment can be explained to some degree by the covariates. Otherwise, the variability only can be explained by random noise and unobserved factors.

An interaction between time and region fixed effects in the individual-level logistic regression model can identify if trends over time and region are linked. Then by calculating the sample variances of region fixed effects for each time period one

can test the region-specific fixed effects for increasing and decreasing variance to look for the S-shaped diffusion process during the sample period.

Table 2-4. Hypothesized Effects of Variables on Probability of Choosing BCS Alone or Mastectomy, 1991-1996.

Variable	Hypothesized Effect on Probability of BCS Alone	Hypothesized Effect on Probability of Mastectomy	Source of Hypothesis
Registry indicator variables	Varies by region	Varies by region	(23,25,27-32,101)
Black race	-	+	(34,42)
Other race besides Black or White	+	+	(42)
Marital status	-	+	Author
Older age	+	+	(25,29,32,34)
Higher comorbidities based on Medicare claims	+	+	(102)
Education level higher at zip-code level	-	-	(37)
Below-poverty percentage higher at zip-code level	-	+	(37)
Rural-residence percentage higher at zip-code level	-	+	(71)
Higher # radiation oncologists per 100,000 residents	-	-	(32)

Assessment of Outcomes

Assessing the impact of treatment choice on outcomes using a large administrative database is the second major analytic component of this study. Studies have shown that the mortality risk from DCIS is low (4) so an appropriate outcome to measure here is recurrence of DCIS or subsequent invasive breast cancer rather than death from DCIS. In this study, outcomes are analyzed semiparametrically using a standard discrete-time duration model with two parameterizations of duration, or elapsed time since diagnosis.

The first part of this section describes the methodological issues related to analyses of observational data and the biases inherent in the present study. The second part discusses in detail the methods used for the outcomes analyses.

Methodological Issues Related to Outcomes Studies

The systematic evaluation comparing BCS, BCS with radiotherapy, and mastectomy for treatment of DCIS via a randomized controlled trial (RCT) would be expensive and time-intensive, and the treatments already are established as effective even if it is unclear which is best (103,104). One can assess already-existing information and data sources in a methodical way, however, to come up with optimal treatment strategies. Wennberg et al. suggest a process to do just this (105).The first step is to evaluate published literature and current opinion to identify hypotheses about how and why physicians practice a certain way and what the controversies are over practices. This will suggest clues as to what might explain differences in

outcomes. Second, one can use large claims databases to obtain probability estimates to look for differences in treatment efficacy and to evaluate potential differences in hospital- or area-specific outcome rates (105).

Outcomes research has shown the value and limitations of claims databases for assessing treatment effectiveness (106). Many of these characteristics hold for registries. Claims data are cheap, allow for long followup, and can be used to obtain information about alternative treatments and recurrence to disease (106). Case-mix and comorbidities may be harder to assess via claims data because patient health status is not directly ascertained in claims data or registries (107), but there are techniques in the literature to obtain comorbidities from claims data (108-110), some which are specific for breast cancer patients (91,111). Incomplete identification of comorbidities may cause some bias in estimating the relationship between treatment and outcomes because selection cannot entirely be eliminated.

The reliance on RCTs for effectiveness data is limited because many RCTs exclude people with certain characteristics such as comorbidities, old age, or other confounding factors, which makes RCTs less generalizable than some might hope (104). Considering that older women have much higher incidence rates of breast cancer, they have especially low participation and are clearly underrepresented in cancer treatment protocols sponsored by the National Cancer Institute (112). Therefore, long-term observational studies of claims databases and registries can provide valuable sources of data to analyze treatment effectiveness across all types of patients.

A goal of this work is to describe transition probabilities (or disease-free survival) after treatment, but there may be bias associated with estimating treatment effects, state-specific transitions, and disease-free survival. Treatments are considered "endogenous" if unobserved factors, such as tumor characteristics, simultaneously affect both treatment choice and outcomes. As a result, typical estimation strategies will yield biased estimates of treatment effects because of a spurious correlation between treatments and outcome (113). For example, women with small or low-grade tumors (measurement of which is not available in the SEER-Medicare data) are more apt to undergo BCS, and they also fare better in terms of lower recurrence rates and longer disease-free survival because they are "healthier" by having lower severity lesions in the first place. This type of correlation with an unmeasured characteristic creates a bias in the estimates of effect sizes and is referred to as endogeneity bias.

In the absence of a RCT, one might assume that assignment to treatment groups is caused by factors that are unobserved in the analysis, leading to endogeneity bias in estimates of treatment effects. Unfortunately, long-term outcomes data from randomized clinical trials are not available to answer the questions posed here. The methods used are intended to limit the bias of the estimates of treatment effects from observational data.

The modeling strategy attempts to explain the variability in women's health status in order to understand how outcomes of different treatments vary. Because some unobserved factors related to health status might vary by geographic area and

these factors could be correlated with treatment rates, geographic fixed effects are incorporated into the model. The fixed effects represent unobserved factors – geographic and possibly other differences – that are constant by region over the time period of the study. For example, if one region has a tendency for women being diagnosed at an earlier point in the disease process, then that region's DCIS lesions will tend to be smaller. This would have an impact on treatment choice and outcomes. Earlier diagnosis is not a variable that can be inserted in the model because such information is not available in the data. The fixed effects should yield less-biased treatment effect estimates because omitted-variables bias is reduced.

Semiparametric Discrete-Time Approach

I use a standard semiparametric discrete-time duration model to operationalize a two-state transition probability model to predict outcomes. The basic element of the model is the transition probability, defined as follows:

$P_i^{\tau} \equiv P[k_i \longrightarrow l_i \mid \tau_i, H_t, X_{it}, Tx_i]$ is the probability that individual i makes the transition from state k to state l after τ periods in state k. Note that P_i indicates the probability of a transition within state to remain disease-free in the next period (k to k) or to a new state having a subsequent breast event in the next period (k to l). The transition probabilities are explicitly conditional on the following variables: τ represents duration in state k, or elapsed time since entering state k; H is a vector of variables that summarize history, or prior experiences in the various states; X_t is a vector of covariates at time t, including socioeconomic and demographic variables,

and geographic region; and *Tx* is a dummy variable indicating treatment type. (See Table 2-5 for hypothesized effects of covariates on the probability of a subsequent breast event.)

Discrete-time transition probability models are typically characterized by hazard functions, duration distributions, and survivor functions. The hazard function, or the probability of leaving state *k* after τ periods, is defined as follows: $H_k(\tau) = 1 - P_{kk}^{\tau}$. The hazard function is state specific (subscripted by *k*) so that a distinct hazard function is associated with both states in the model. The duration distribution gives the distribution of spell lengths, or continuous years within a state. It is given by $f_k = (1 - P_{kk}^{\tau}) * S_k(\tau - 1)$, where $S_k(\tau\text{-}1)$ is the survivor function defined as $S_k(\tau - 1) = \prod_{t=1}^{\tau-1} P_{kk}^{t}$.

The transition probabilities, P_i, for the two states, disease free or experiencing a subsequent breast event, are estimated as a logit, censoring those who die from non-breast cancer causes or survive the entire period without a breast event. The logit specification of P_i has several advantages. First, it allows for construction of hazard functions, survivor functions, and duration distributions so that results can be summarized and presented using these common tools. Second, it allows for a fully-nonparametric specification of the baseline hazard function by including a vector of duration-effect indicator variables that spans τ. This yields a distinct baseline hazard for each treatement strategy. Finally, the model allows for interactions between duration effects and treatment covariates. Thus, the model is not

restricted to a class known as proportional hazards models. The model allows a characteristic to increase the hazard function for low values of τ, and decrease the hazard function for higher values of τ. For example, a younger woman might be more likely to have an aggressive cancer, which could increase her risk of a subsequent breast event in the period shortly after treatment. If she were to survive in the state for 5 or more years, however, her younger age might result in a relatively lower risk of a subsequent breast event compared to an older woman.

Using a nonparametric approach is flexible and allows the data to define their shape rather than imposing perhaps inappropriate structure on the data by making certain assumptions about their patterns or distributions. Nonparametric estimation can also inform a parametric and more parsimonious model. To allow for a model to be as nonparametric as possible while still obtaining convergence through a maximum likelihood model (logit), the baseline hazard is fully nonparametric but most of the covariates (all except the treatment variables) assume proportional hazards. By estimating a logit model for each treatment, each treatment type is fully-interacted in the model and the model specification can be slightly different for each treatment if necessary. In addition, a model with the treatment variables interacted with the covariates allows one to test if the set of treatment interactions is significantly different from zero, and therefore whether the treatment arms are statistically different from each other in terms of disease-free survival.

In all models, cases are censored if a patient is still alive and has not succumbed to a subsequent breast event at the end of the observation time, if a

patient enrolls in an HMO, or if a patient dies of a non-breast-cancer cause. An "exit," the dependent variable, is defined as a case that succumbs to a subsequent breast event. Because there are multiple observations per individual (one for each year the patient is alive and does not have a subsequent breast event), Huber-White robust standard errors are implemented (114).

In addition to a model with nonparametric duration variables (dummy variable for each time period), a more parsimonious model is estimated with a polynomial, tau (i.e., with term tau with values ranging from 1 to 7, i.e., the length of time a case is observed). This specification is used because the nonparametric specification of duration suggested that there is a fairly linear relationship between duration and the probability of a subsequent breast event.

Including fixed effects in the model should reduce omitted-variables bias. There are two ways to do this: 1) region-specific fixed effects, which assumes the unobserved variables that are related to treatment and outcomes are constant within region over time; and 2) region-specific polynomials in time, which assumes there are region-specific trends in the unobserved factors that are related to treatment choice. Variation in region-specific treatment rates from the modeled fixed effects will allow for less-biased estimates of treatment effects in the transition probabilities.

From the estimates of the discrete-time duration models, one can obtain overall hazard rates across all individuals for each time period t for each treatment Tx, $P_{t,Tx}$, conditional on surviving disease-free in the prior period. The hazard rates can be transformed simply into disease-free survival rates for each treatment: $S_{t,Tx}$

$=1-P_{t,Tx}$ in the first period ($t=1$), where $P_{t,Tx}$ is the population probability of a subsequent breast event (or hazard rate). In later periods, survival is estimated as $S_{t,Tx}$ $=S_{t-1,Tx}*(1-P_{t,Tx})$ because it is dependent on surviving disease free in the prior period. The difference in disease-free survival across treatment types is calculated as the area between two survival curves, or the sum of the differences between each $S_{t,Tx}$ for each treatment at each time period (($S_{t(BCS)} - S_{t(mastectomy)}$), ($S_{t(BCS)} - S_{t(BCS\ with\ radiotherapy)}$), and ($S_{t(BCS\ with\ radiotherapy)} - S_{t(mastectomy)}$)). That survival difference is then bootstrapped to identify if the difference between each pair of curves is significant.

Table 2-5. Hypothesized Effects of Variables on DCIS Treatment Outcomes, 1991-1998.

Variable	Probability of Subsequent Breast Event	Source or Reason
BCS alone	Unknown	
BCS and radiotherapy	Lower compared to BCS alone	(15,115)
Registry indicator variables	None	Only affect treatment choice
Black	Higher	May present with more severe disease
Other race	Unknown	
Married	Lower	Social support
Older age	Lower	(115)
Comorbidities (mastectomy-only model)	Lower	Die of other cause first
Educational attainment higher	Lower	Better access to care
Below-poverty percentage higher	Higher	Problems with access to care
Rural-residence percentage higher	Higher	Problems with access to care

Parametric Survival Model

Parametric survival analysis, where "survival" is actually disease-free time, imposes more structure on the data but allows for a more parsimonious model based on assumptions about the underlying distribution of the data. In addition, a parametric structure can be placed on any unobserved heterogeneity (i.e., frailty) in order to account for it in the model. The unobserved heterogeneity is actually integrated out of the equation during estimation.

Unfortunately, the parametric survival models attempted in this study were too sensitive to specifications of the underlying distribution and would not converge to meaningful results.

Software

All analyses use Stata statistical software, release 7.0 (StataCorp, College Station, TX). Much of the initial data management uses SAS versions 6 and 8 (Cary, NC).

Chapter 3

Results

This chapter is divided into two parts. The first part discusses results for the geographic variations analysis, and the second shows the results of the outcomes analyses. The samples from the data base are different for each analysis, as described in Chapter 2.

Geographic Variations Results

The sample for the analysis of geographic variations consists of 2,701 women diagnosed with unilateral DCIS from 1991-1996, 1,044 (39%) of whom underwent BCS alone, 681 (25%) who received BCS with radiotherapy, and 976 (36%) who underwent mastectomy. The characteristics of these women are shown in Table 3-1. In the bivariate analysis there were statistically significant differences in treatment at or below the 10% level across age categories, registries, race, marital status, and percentages rural, below poverty, and without a high school education. The majority of women in the sample were under age 75 years (57% of BCS alone, 78% of BCS with radiotherapy, and 67% of mastectomy patients). The San Francisco metropolitan area registry had the highest percentage of patients undergoing BCS alone (56%); the Connecticut registry had the highest percentage of women receiving BCS with radiotherapy (43%); and the Iowa registry had the most undergoing mastectomy (51%). Of those receiving BCS alone, 57% were unmarried, compared to 45% of those undergoing BCS with radiotherapy. Overall, 83% of the sample was

white. Of all cases, 96% had an inpatient claims comorbidity index of 0 or below, and 95% had a physician claims comorbidity index of 0 or below which indicates that almost the entire sample had no comorbidities expected to affect non-cancer mortality and potentially treatment choice.

The Census variables at the zip-code level showed statistically significant differences across treatment groups. The majority of cases lived in zip-code areas that have no rural base (62% with 0% rural population; mean 11%, range 0-100%). The percentage without a high school diploma is highest where educational attainment is lowest; the variable is broken into quintiles for analysis, but as a continuous variable, it has a mean of 20% and a range of 0-76%. The percentage living below the poverty level is highest in the poorest zip-code areas, and its mean is 10% with a range of 0-56%. The number of radiation oncologists per 100,000 population in the hospital service area varies from 1.24 for mastectomy to 1.29 for BCS with radiotherapy to 1.36 for BCS alone.

In the bivariate analysis the chi-square test for differences in treatment by registry yielded a value of 195.66 ($p=0.000$), which shows overwhelmingly that there are significant differences in treatments across registries.

The multinomial logistic regression model for geographic variations analysis includes indicators for all registries, age, race, and marital status categories, continuous variables for the comorbidity indices, and zip-code level indicator variables for quintiles of poverty level and educational attainment, and categories of the percentage rural population. Finally, one hospital-service area level variable for

the number of radiation oncologists per 100,000 population is included in the model. The possible outcomes are BCS, BCS with radiotherapy, and mastectomy.

Tests of the model include one for multicollinearity and another for the independence of irrelevant alternatives. The median income variables had high variance inflation factors, indicating multicollinearity. They were highly correlated with poverty and education, so they were excluded in the model. The independence of irrelevant alternatives (IIA) assumption was met, as the Hausman test showed no evidence that IIA was violated (X^2 for test that the difference in coefficients is not systematic=14.22 (p=0.9993 with 35 degrees of freedom)).

The multinomial logit model coefficient estimates show that the following are significant in predicting use of BCS with radiotherapy relative to BCS alone at the 10% level: 9 registries of San Francisco, Detroit, Michigan, Iowa, New Mexico, Seattle, Utah, Atlanta, Georgia, San Jose, and Los Angeles, year of diagnosis of 1993-1996, marital status, age group, and percentage rural in the zip-code area. The following are significant in explaining the use of mastectomy: 6 registries of San Francisco, Hawaii, Iowa, New Mexico, Utah, Atlanta, Georgia, year of diagnosis, marital status, age, other race or ethnicity, radiation oncologists per 100,000 population, and percentage without a high school education in the zip-code area. See Table 3-2 for the coefficient estimates of the model.

To assess the impact of different variables on treatment choice, the expected probabilities of each treatment are predicted after changing covariate values one-by-one. In the multivariate assessment of geographic variations, the multinomial logistic

regression results showed that in the reference case (Connecticut registry, ages 65-69, diagnosis year of 1991, white race, unmarried, lowest poverty, most educated, mean number of radiation oncologists per 100,000 population, and no rural population), the expected percentage undergoing BCS alone is 25% and percentage undergoing BCS with radiotherapy is 46%. In San Francisco, this changes to 46% undergoing BCS alone and 15% undergoing BCS with radiotherapy. Table 3-3 shows the predicted probabilities of treatment choice given different characteristics, including the shifts for each registry.

As age increases, so does the probability of undergoing BCS alone, from 25% in the reference case (ages 65-69), to 29% for ages 70-74, to 36% for ages 75-79, and to 47% for those ages 80 and over. The probability of undergoing BCS with radiotherapy decreases with age, and the probability of receiving mastectomy has no clear trend by age.

Compared to the reference case, black women are predicted to be less likely to undergo BCS alone (20%) and are more likely to receive BCS with radiotherapy (51%) or mastectomy (29%). Women of "other" races or ethnicities are much more likely to undergo mastectomy compared to the base case (38% vs. 31% in the reference case). Married women are slightly more likely to undergo BCS with radiotherapy (51%), and slightly less likely to undergo BCS alone (20%).

Cases in the zip-code areas with the highest quintile of those without a high school education are much more likely to undergo mastectomy (40% compared to 31% in the reference case). Likewise, women in areas with the highest percentage

rural are much more likely to undergo mastectomy (40%) compared to the reference case (30%), but much less likely to undergo BCS with radiotherapy (36% vs. 46% for reference case).

Interestingly, when the number of radiation oncologists is increased to the 90th percentile value from the median value, the probability of a women undergoing BCS with radiotherapy increases only by 0.6% to 46.1% compared to the median value. The probability of receiving mastectomy, the model in which the radiation-oncologist variable was significant, decreases slightly to 28% from 30%.

After bootstrapping the standard errors of the probability of choosing a particular treatment to determine the average variation in treatment choice across regions, the covariates beyond the registry indicators in the multinomial logit model explain very little of the variation in treatment choice. The point estimates are almost identical after adding the demographic covariates, but the confidence intervals actually get wider. Almost all of the variation is unexplainable. (See Table 3-4.) The decrease in the sample standard error after the demographic covariates are added to the model is 14.7% for mastectomy, 9% for BCS with radiotherapy, and only 1% for BCS alone.

In evaluating whether variation in treatment choice is increasing or decreasing over time by calculating the sample standard deviations of the region fixed effects for each time period, all indications are that the sample standard deviations are increasing. By the end of the final time period after diagnosis (6.5 years after diagnosis), however, the sample standard deviations for BCS alone and

BCS with mastectomy drop slightly. (See Figure 3-1.) This suggests that during the study period there is increasing uncertainty, and therefore increasing variability, in treatment choice until the last time period. This trend holds whether or not the demographic covariates are in the model. If the S-shaped curve of the diffusion process holds, the variance of treatment probabilities would form an upside-"U" shape over time. The findings of this study suggest that we may be in the accelerating, increasing phase of adoption of BCS alone and BCS with radiotherapy, which corresponds to moving towards the top of the "U" from the left. The confidence intervals of the sample standard deviations were bootstrapped, however, and were quite wide, yielding only weak evidence of this trend.

Table 3-1. Initial Treatment Type and Comparison of Means of Demographic Factors for Geographic Variations Analysis based on Linked SEER-Medicare database, 1991-1996 (n=2701).

	Breast-conserving surgery	Breast-conserving surgery with radiotherapy	Mastectomy	
Treatment	1044 (39)	681 (25)	976 (36)	2701
Individual-Level Variables				**X^2 for difference**
Age in Years, n(% of treatment group in age category)				102.51 (p=0.000)
65-69	290 (28)	304 (45)	347 (36)	
70-74	303 (29)	227 (33)	302 (31)	
75-79	223 (21)	96 (14)	192 (20)	
80+	228 (22)	54 (8)	135 (14)	
Registry, n (% in registry receiving treatment)				195.24 (p=0.000)
San Francisco	194 (56)	59 (17)	91 (26)	
Connecticut	112 (31)	154 (43)	93 (26)	
Detroit	138 (35)	122 (31)	137 (35)	
Hawaii	28 (21)	52 (39)	53 (40)	
Iowa	83 (30)	50 (18)	140 (51)	
New Mexico	34 (30)	26 (23)	52 (46)	
Seattle	91 (38)	57 (24)	90 (38)	
Utah	24 (34)	15 (21)	31 (44)	
Atlanta	52 (36)	28 (19)	66 (45)	
San Jose	54 (42)	24 (18)	52 (40)	
Los Angeles	234 (47)	94 (19)	171 (34)	
Marital Status, n(% of treatment group in marital category)				23.91 (p=0.000)
Not married	590 (57)	304 (45)	490 (50)	
Married	454 (43)	377 (55)	486 (50)	
Race/Ethnicity, n(% of treatment group in race category)				8.82 (p=0.066)
White	896 (86)	557 (82)	800 (82)	
Black	76 (7)	55 (8)	79 (8)	
Other*	72 (7)	69 (10)	97 (10)	
Inpatient Claims Comorbidity Index, n(% of treatment group in index category)				2.26 (p=0.688)
Index<=0	1013 (97)	655 (96)	937 (96)	
index<=0.83 & index>0	17 (2)	14 (2)	24 (2)	
Index>0.83	14 (1)	12 (2)	15 (2)	
Physician Claims Comorbidity Index, n(% of treatment group in index category)				3.70 (p=0.449)
Index<=0	981 (94)	648 (95)	930 (95)	
index<=0.65 & index>0	32 (3)	18 (3)	29 (3)	
Index>0.65	31 (3)	15 (2)	17 (2)	

Table 3.1 – continued. Initial Treatment Type and Comparison of Means of Demographic Factors for Geographic Variations Analysis based on Linked SEER-Medicare database, 1991-1996 (n=2701).

	Breast-conserving surgery	Breast-conserving surgery with radiotherapy	Mastectomy	
Variables based on zip-code area				**X^2 for difference**
Percentage Living in Rural Area, n(%)				21.47 (p=0.002)
% rural=0	677 (65)	453 (67)	570 (58)	
% rural>0 & % rural<10	181 (17)	94 (14)	171 (18)	
% rural>=10 & % rural<50	112 (11)	83 (12)	129 (13)	
% rural>=50	74 (7)	51 (7)	106 (11)	
Percentage without High School Diploma, n(%)				16.78 (p=0.032)
Lowest 20%	236 (23)	143 (21)	173 (18)	
Second quintile	208 (20)	142 (21)	174 (18)	
Third quintile	217 (21)	140 (21)	199 (20)	
Fourth quintile	189 (18)	135 (20)	214 (22)	
Highest 20%	194 (19)	121 (18)	216 (22)	
Percentage Living under Poverty Level, n(%)				30.30 (p=0.000)
Lowest 20%	213 (20)	183 (27)	180 (18)	
Second quintile	218 (21)	145 (21)	193 (20)	
Third quintile	215 (21)	133 (20)	182 (19)	
Fourth quintile	211 (20)	117 (17)	203 (21)	
Highest 20%	187 (18)	103 (15)	218 (22)	
Variable based on hospital service area				
Radiation oncologists per 100,000 population				
Mean	1.36	1.29	1.24	
Standard Deviation	0.67	0.64	0.59	
Median	1.29	1.23	1.18	

Note: Inpatient comorbidity index median is 0.83 when excluding negative and zero values for index. Outpatient comorbidity index median is 0.65 when excluding negative and zero values for index.

*Other race/ethnicity refers to patients who were classified as neither white nor black. Columns for each variable may not add to 100% due to rounding errors.

Table 3-2. Multinomial Logit Model Coefficient Estimates for Probability of Treatment Choice Compared to Breast-conserving Surgery Alone, 1991-1996 (n=2701).

	Coefficient	Standard Error	z	P>|z|	95% Confidence Interval	
Treatment 1 (BCS with radiotherapy)						
San Francisco	-1.7103	0.2278	-7.51	0.000	-2.1568	-1.2638
Detroit	-0.6544	0.1957	-3.34	0.001	-1.0380	-0.2709
Hawaii	0.0317	0.3387	0.09	0.925	-0.6320	0.6954
Iowa	-0.6377	0.2579	-2.47	0.013	-1.1433	-0.1322
New Mexico	-0.6405	0.3241	-1.98	0.048	-1.2757	-0.0053
Seattle	-0.9371	0.2473	-3.79	0.000	-1.4217	-0.4525
Utah	-0.9781	0.3863	-2.53	0.011	-1.7353	-0.2210
Atlanta	-1.2433	0.2911	-4.27	0.000	-1.8139	-0.6727
San Jose	-1.2174	0.2971	-4.10	0.000	-1.7997	-0.6351
Los Angeles	-1.4861	0.2091	-7.11	0.000	-1.8958	-1.0764
1992	0.2231	0.2098	1.06	0.288	-0.1881	0.6343
1993	0.3791	0.2039	1.86	0.063	-0.0204	0.7787
1994	0.5439	0.2006	2.71	0.007	0.1507	0.9371
1995	0.4366	0.1968	2.22	0.027	0.0508	0.8224
1996	0.4693	0.1962	2.39	0.017	0.0847	0.8539
radiation oncologists	-0.0574	0.0879	-0.65	0.514	-0.2297	0.1149
marital status	0.2962	0.1087	2.73	0.006	0.0833	0.5092
Age 70-74	-0.2717	0.1250	-2.17	0.030	-0.5168	-0.0266
Age 75-79	-0.8256	0.1536	-5.37	0.000	-1.1267	-0.5245
Age 80+	-1.3853	0.1818	-7.62	0.000	-1.7415	-1.0290
Black	0.3309	0.2224	1.49	0.137	-0.1050	0.7667
Other race	0.0518	0.2399	0.22	0.829	-0.4183	0.5220
Comorbidity (physician claims)	-0.2387	0.2796	-0.85	0.393	-0.7866	0.3092
Comorbidity (inpatient claims)	0.2046	0.2568	0.80	0.426	-0.2987	0.7079
2nd poverty quintile	0.0889	0.1689	0.53	0.599	-0.2421	0.4199
3rd poverty quintile	0.0061	0.1882	0.03	0.974	-0.3629	0.3750
4th poverty quintile	-0.0009	0.2138	0.00	0.997	-0.4199	0.4182
5th poverty quintile	-0.1411	0.2615	-0.54	0.590	-0.6537	0.3715
2nd education quintile	-0.1019	0.1688	-0.60	0.546	-0.4327	0.2288
3rd education quintile	-0.1924	0.1797	-1.07	0.284	-0.5446	0.1598
4th education quintile	-0.1560	0.1991	-0.78	0.433	-0.5463	0.2343
5th education quintile	-0.1691	0.2469	-0.68	0.493	-0.6531	0.3148
% rural>0 & % rural<10	-0.4708	0.1621	-2.90	0.004	-0.7886	-0.1530
% rural>=10 & % rural<50	-0.3347	0.1895	-1.77	0.077	-0.7062	0.0367
% rural>=50	-0.4633	0.2210	-2.10	0.036	-0.8964	-0.0301
constant	0.6892	0.2827	2.44	0.015	0.1351	1.2433

Table 3-2 – continued. Multinomial Logit Model Coefficient Estimates for Probability of Treatment Choice Compared to Breast-conserving Surgery Alone, 1991-1996.

	Coefficient	Standard Error	z	P>|z|	95% Confidence Interval	
Treatment 2 (Mastectomy)						
San Francisco	-0.3596	0.2162	-1.66	0.096	-0.7834	0.0642
Detroit	0.2570	0.2002	1.28	0.199	-0.1353	0.6494
Hawaii	0.6670	0.3262	2.05	0.041	0.0277	1.3063
Iowa	0.8441	0.2309	3.66	0.000	0.3916	1.2967
New Mexico	0.6579	0.2926	2.25	0.025	0.0844	1.2313
Seattle	0.4276	0.2335	1.83	0.067	-0.0300	0.8852
Utah	0.6641	0.3329	1.99	0.046	0.0116	1.3166
Atlanta	0.5646	0.2530	2.23	0.026	0.0687	1.0605
San Jose	0.3741	0.2579	1.45	0.147	-0.1314	0.8796
Los Angeles	-0.0751	0.2015	-0.37	0.709	-0.4699	0.3198
1992	-0.3162	0.1627	-1.94	0.052	-0.6350	0.0026
1993	-0.5532	0.1653	-3.35	0.001	-0.8771	-0.2293
1994	-0.4441	0.1632	-2.72	0.007	-0.7639	-0.1242
1995	-0.6004	0.1602	-3.75	0.000	-0.9145	-0.2864
1996	-0.7919	0.1641	-4.82	0.000	-1.1136	-0.4702
radiation oncologists	-0.1557	0.0813	-1.91	0.056	-0.3151	0.0038
Marital status	0.1597	0.0970	1.65	0.100	-0.0303	0.3498
Age 70-74	-0.1937	0.1177	-1.65	0.100	-0.4243	0.0370
Age 75-79	-0.2670	0.1322	-2.02	0.044	-0.5261	-0.0078
Age 80+	-0.6190	0.1437	-4.31	0.000	-0.9007	-0.3373
Black	0.2321	0.1968	1.18	0.238	-0.1536	0.6177
Other race	0.3869	0.2037	1.90	0.058	-0.0124	0.7861
Comorbidity (physician claims)	-0.4232	0.2591	-1.63	0.102	-0.9311	0.0847
Comorbidity (inpatient claims)	0.2608	0.2363	1.10	0.270	-0.2022	0.7239
2nd poverty quintile	0.0223	0.1570	0.14	0.887	-0.2854	0.3300
3rd poverty quintile	-0.2251	0.1727	-1.30	0.192	-0.5637	0.1134
4th poverty quintile	-0.2582	0.1907	-1.35	0.176	-0.6319	0.1155
5th poverty quintile	0.0000	0.2268	0.00	1.000	-0.4446	0.4446
2nd education quintile	0.0829	0.1561	0.53	0.595	-0.2230	0.3888
3rd education quintile	0.1554	0.1633	0.95	0.341	-0.1646	0.4754
4th education quintile	0.2789	0.1780	1.57	0.117	-0.0699	0.6278
5th education quintile	0.3520	0.2140	1.64	0.100	-0.0674	0.7714
% rural>0 & % rural<10	-0.0543	0.1400	-0.39	0.698	-0.3288	0.2201
% rural>=10 & % rural<50	-0.1088	0.1720	-0.63	0.527	-0.4460	0.2285
% rural>=50	0.1926	0.1904	1.01	0.312	-0.1805	0.5657
constant	0.3904	0.2587	1.51	0.131	-0.1166	0.8973

Note: Bold indicates significant at 10% level.
Note: The 5th poverty quintile refers to the highest quintile of percentage of persons living below the poverty level, or the poorest quintile. The 5th education quintile refers to the highest quintile of percentage without a high school education, or the least-educated quintile.

Table 3-3. Predicted Percentage Use of Initial Treatment for Ductal Carcinoma in Situ, Based on Linked SEER-Medicare Database, 1991-1996 (n=2701).

	BCS alone	BCS w/XRT	Mastectomy
Reference case	24.5	45.5	29.9
San Francisco	45.7	15.3	38.9
Detroit, Michigan	28.2	27.2	44.5
Hawaii	18.9	36.2	44.9
Iowa	20.7	20.4	58.9
New Mexico	23.1	22.6	54.4
Seattle	27.8	20.2	52.0
Utah	24.6	17.2	58.3
Atlanta, Georgia	27.2	14.5	58.3
San Jose	30.1	16.5	53.4
Los Angeles	39.2	16.5	44.4
ages 70-74	29.2	41.4	29.4
ages 75-79	36.4	29.6	34.0
ages 80+	47.1	21.9	31.0
Married	20.3	50.7	29.1
Black	19.5	50.4	30.0
Other race	21.0	41.1	37.8
2nd poverty quintile	23.4	47.4	29.2
3rd poverty quintile	26.0	48.6	25.4
4th poverty quintile	26.3	48.8	24.8
5th poverty quintile	26.1	42.1	31.8
4th education quintile	23.8	37.8	38.4
5th education quintile	23.2	36.4	40.3
rural>=50%	27.4	32.0	40.6
Radiation oncologists at 90th percentile	26.1	46.1	27.8

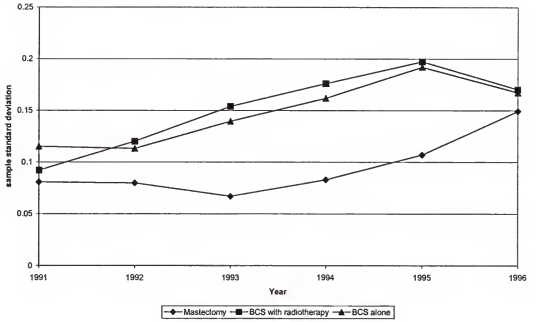
Note: The reference case is the Connecticut registry, ages 65-69, diagnosis year of 1991, white race, unmarried, lowest poverty quintile, lowest percentage without a high school diploma (most educated quintile), mean radiation oncologist rate, and 0% rural population.
Note: The 5th poverty quintile refers to the highest quintile of percentage of persons living below the poverty level, or the poorest quintile. The 5th education quintile refers to the highest quintile of percentage without a high school education, or the least-educated quintile.

Table 3-4. Observed Sample Standard Errors and Confidence Intervals for Probability of Choosing Treatment Option Obtained by Bootstrapping 400 Times.

	Observed sample standard deviation	95% Confidence interval	
Model with covariates			
BCS alone	0.091	0.0631	0.1198
BCS with radiotherapy	0.060	0.0149	0.1049
Mastectomy	0.058	0.0321	0.0846
Model without covariates			
BCS	0.092	0.0737	0.1110
BCS with radiotherapy	0.066	0.0453	0.0862
Mastectomy	0.068	0.0487	0.0877

Note: These estimates were obtained by predicting the probability of treatment choices based on standardized populations for each registry. Using the average effects by region, the sample standard deviation for each treatment is bootstrapped to estimate a confidence interval around the statistic.

Figure 3-1. Standard Deviation of Treatment Probability Across Registries, by Treatment Strategy and Year



Outcomes Analysis Comparing BCS, BCS with Radiotherapy, and Mastectomy

The sample for the analysis of outcomes for all three treatment regimens consists of 2,192 women with unilateral DCIS diagnosed from 1991-1996, 824 (38%) of whom underwent BCS alone, 566 (26%) who received BCS with radiotherapy, and 802 (37%) who underwent mastectomy. (See Table 3-5.) The unadjusted rates of subsequent breast events for these cases vary significantly by treatment, with 13% of women undergoing BCS, 6% of BCS-with-radiotherapy patients, and 4% of mastectomy patients (X^2=44.52, p=0.000). The demographic characteristics of these women are shown in Table 3-6. The bivariate analysis showed statistically significant differences in treatment by age categories, registries, marital status, and year of diagnosis. Similar to the geographic variations analytic sample, the majority (65%) of women in this sample were under age 75 years. The San Francisco metropolitan area registry again had the highest percentage of patients undergoing BCS alone (56%), followed by the Los Angeles metropolitan area registry (47%); the Connecticut registry had the highest percentage of women receiving BCS with radiotherapy (43%), followed by the Hawaii registry (40%); and the New Mexico registry had the most undergoing mastectomy (56%), followed by the Iowa registry (50%).

Of those receiving BCS alone, 58% were unmarried, compared to 46% of those undergoing BCS with radiotherapy, and 51% undergoing mastectomy. There were significant differences by treatment group in year of diagnosis (p=0.000), with the percentage undergoing BCS alone starting at 33% in 1991 and increasing to 41%

by 1996. Similarly, there was an increase in the use of BCS with radiotherapy from 18% to 31%. Mastectomy decreased in use from 49% in 1991 to 27% in 1996. There were no statistically significant differences across race/ethnic categories in the sample (X^2=6.59, p=0.159), with 8% of the sample black and 7% of "other" races or ethnicities (all categories excluding black and white).

The multivariate models for outcomes analysis of the three treatment strategies include indicator variables for the SEER registries (representing geographic region), age, and marital status, except that age and marital status were excluded from the estimation of outcomes following treatment by mastectomy. The first model is semiparametric and includes dummy variables for each year elapsed since diagnosis that a patient is in the data set as alive without experiencing a subsequent breast event. The second model instead incorporates a parametric duration variable, tau, which takes on values of 1 to 7, depending on how long the person is alive and disease-free. This parametric restriction on duration provides for a more parsimonious model to characterize the hazard function. Because of some blank cells, that is, small numbers in certain cross-tabulations, registry 6 (New Mexico) had to be dropped as an independent variable.

Table 3-5. Initial Treatment Type and Subsequent Breast Events for Women Diagnosed with DCIS in Final Outcomes-Analysis Sample from Linked SEER-Medicare Database, 1991-1996.

	No Subsequent Breast Event	Subsequent Breast Event, n (%)	Total
Breast-conserving surgery	718	106 (13)	824
Breast-conserving surgery with radiotherapy	531	35 (6)	566
Mastectomy	768	34 (4)	802
Total	2017	175 (8)	**2192**
X^2 for difference			44.52 (p=0.0000)

Table 3-6. Initial Treatment Type and Comparison of Demographic Factors for Outcomes Analysis based on Linked SEER-Medicare Database, 1991-1996 (n=2192).

	Breast-conserving surgery	Breast-conserving surgery with radiotherapy	Mastectomy	
Individual-Level Variables				**X^2 for difference**
Age in Years, n (% of treatment group in age category)				105.62 (p=0.000)
65-69	218 (26)	259 (46)	286 (36)	
70-74	237 (29)	191 (34)	239 (30)	
75-79	177 (21)	72 (13)	159 (20)	
80+	192 (23)	44 (8)	118 (15)	
Registry, n (% in registry receiving treatment)				170.94 (p=0.000)
San Francisco	119 (57)	33 (16)	58 (28)	
Connecticut	109 (31)	153 (43)	92 (26)	
Detroit	142 (36)	120 (30)	138 (35)	
Hawaii	17 (21)	32 (40)	31 (39)	
Iowa	84 (31)	52 (19)	138 (50)	
New Mexico	21 (23)	19 (21)	50 (56)	
Seattle	77 (41)	34 (18)	75 (40)	
Utah	23 (38)	12 (20)	26 (43)	
Georgia	51 (35)	28 (19)	66 (46)	
San Jose	43 (44)	16 (15)	38 (39)	
Los Angeles	138 (47)	67 (23)	90 (31)	
Marital Status, n (% of treatment group in marital category)				20.93 (p=0.000)
Not married	476 (58)	258 (46)	406 (51)	
Married	348 (42)	308 (54)	396 (49)	
Race/Ethnicity, n(%)				6.59 (p=0.159)
White	721 (88)	470 (83)	674 (84)	
Black	54 (7)	47 (8)	64 (8)	
Other*	49 (6)	49 (9)	64 (8)	
Year of diagnosis, n (% by year receiving treatment)				44.12 (p=0.000)
1991	110 (33)	61 (18)	162 (49)	
1992	138 (38)	79 (22)	146 (40)	
1993	130 (38)	94 (27)	122 (35)	
1994	134 (36)	100 (27)	137 (37)	
1995	154 (39)	112 (28)	130 (33)	
1996	158 (41)	120 (31)	105 (27)	
Years of follow-up				
Mean (overall=4.35)	4.04	4.25	4.74	
Standard deviation	1.90	1.75	1.96	

*Other race/ethnicity refers to patients who were classified as neither white nor black.
Percentages for each variable may not add to 100% due to rounding errors.

Both models censor deaths from other causes, patients who remain alive without succumbing to a subsequent breast event, and patients enrolling in an HMO during followup. The "exit" in the model, or the dependent variable, is a subsequent breast event. Because there is an observation for each year a patient is alive without experiencing a subsequent breast event, Huber-White standard errors are estimated as part of the model, with clustering by individual. The reference case is a nonmarried women in the Connecticut registry aged 65-69 years old.

The semiparametric outcomes model has several variables with statistical significance at the 10% level, depending on which treatment was estimated. For BCS alone, the duration variables and the Los Angeles registry are significant, with the Los Angeles registry yielding a higher rate of subsequent breast events following treatment, all things equal. (See Tables 3-7.) The estimation of outcomes associated with BCS with radiotherapy show that older age and undergoing treatment in the San Francisco registry are linked to higher rates of subsequent breast events, all things equal. Finally, undergoing mastectomy in the Detroit registry is associated with higher rates of subsequent breast events. Another finding is that race, poverty, educational attainment, percentage rural, and median income play no significant role statistically in explaining outcomes and that is why it is dropped from the model. As discussed in the bivariate analysis, there was no significant difference in use of treatments across race categories.

The semiparametric model that includes a duration variable taking on values from 1 to 7 for each year a patient remains in the database alive without experiencing

a subsequent breast event (that is, tau as a single duration variable rather than T1-T7) has many of the same coefficients statistically significant at the 10% level compared to the model with nonparametric duration indicators. (See Table 3-8.) The Los Angeles metropolitan area registry again is significant and associated with higher rates of subsequent breast events after BCS alone. This model shows that women undergoing radiotherapy in addition to BCS have a higher probability of subsequent breast events if they are of younger age or married. There are no significant coefficients in the analysis of treatment by mastectomy except for duration and the constant.

From each of these semiparametric models, it is simple to predict the hazard rate, or risk of a subsequent breast event, for each time period. This is done by predicting the outcome at the mean value of all the covariates except for the treatment variables. The treatment covariates are varied depending on which treatment is being predicted. As seen in Table 3-9, the values are quite close regardless of which semiparametric model is used. BCS at the end of period 1 has an expected 5% rate of subsequent breast events, compared to BCS with radiotherapy or mastectomy which each have approximately a 1% rate. Conditional on not experiencing a subsequent breast event in the first 6 periods, the rates go down quite dramatically, to less than 1% for all three treatment strategies at period 7. Figures 3-1 and 3-3 graphically represent the hazard rates for each model.

The disease-free survival probabilities are easily calculable from the estimated hazard rates. Table 3-9 shows that at the end of period 1 the probability of

living disease-free following BCS is about 95%, whereas for mastectomy or BCS with radiotherapy, the probability is about 99%. The difference is more striking by the end of period 7, when the probability of disease-free survival following BCS is 85% compared to 94% for BCS with radiotherapy and 95% for mastectomy.[6] Figures 3-2 and 3-4 display the disease-free survival rates for both models.

To ascertain if the differences in survival over the study period and given a particular treatment are statistically significantly different from each other, the survival differences over the 7 years of data were bootstrapped 100 times. (See Table 3-10.) Over the time period of the study, BCS with radiation was expected to yield an additional half-year of disease-free survival compared to BCS alone. Mastectomy also showed better disease-free survival than BCS alone, with 0.70 years additional disease-free time. Finally, mastectomy appears slightly better than BCS with radiotherapy because the difference in disease-free survival is 0.14 years in favor of mastectomy, but the 95% confidence interval is quite wide. This means that mastectomy could be better by as much as 0.39 years in terms of disease-free survival or it could be inferior by 0.12 years compared to BCS with radiotherapy.

[6] Data were available for mastectomy only from 1986-1998 and showed nearly identical hazard and survival rates for the first 7 periods as compared to the data from 1991-1998 in this analysis. The rates stay about the same in the final 5 years of mastectomy-only data. The coefficient estimates become somewhat more precise due to the additional observations. See Appendix B.

Table 3-7. Coefficient Estimates from Semiparametric Outcomes Model with Indicators for Each Time Period.

	Coefficient	Standard Error	z	P>|z|	Confidence Interval	
BCS Only						
T1	2.9845	1.0108	2.95	0.00	1.0033	4.9657
T2	2.5840	1.0179	2.54	0.01	0.5889	4.5792
T3	2.2267	1.0295	2.16	0.03	0.2089	4.2445
T4	2.0363	1.0510	1.94	0.05	-0.0236	4.0961
T5	1.8960	1.0806	1.75	0.08	-0.2219	4.0139
San Francisco	0.2262	0.4090	0.55	0.58	-0.5753	1.0278
Detroit	-0.0980	0.4133	-0.24	0.81	-0.9080	0.7121
Hawaii	-0.6119	1.0754	-0.57	0.57	-2.7196	1.4958
Iowa	0.4587	0.4140	1.11	0.27	-0.3527	1.2702
New Mexico	0.6575	0.6077	1.08	0.28	-0.5336	1.8487
Seattle	0.3464	0.4302	0.81	0.42	-0.4968	1.1896
Utah	0.8527	0.5502	1.55	0.12	-0.2257	1.9310
Georgia	0.3895	0.5022	0.78	0.44	-0.5949	1.3738
San Jose	0.8995	0.4549	1.98	0.05	0.0080	1.7910
Los Angeles	0.2277	0.3881	0.59	0.56	-0.5329	0.9884
Age 70-74	-0.2419	0.2595	-0.93	0.35	-0.7504	0.2667
Age 75-79	-0.1991	0.2745	-0.73	0.47	-0.7372	0.3389
Age 80+	-0.4842	0.3187	-1.52	0.13	-1.1089	0.1405
marital	0.2891	0.2071	1.40	0.16	-0.1169	0.6951
constant	-6.0333	1.1021	-5.47	0.00	-8.1934	-3.8732
BCS with Radiation						
T1	0.4483	1.0830	0.41	0.68	-1.6743	2.5709
T2	0.1328	1.1119	0.12	0.91	-2.0465	2.3121
T3	0.6371	1.0929	0.58	0.56	-1.5050	2.7792
T4	-0.2484	1.1887	-0.21	0.84	-2.5782	2.0815
T5	0.1829	1.1708	0.16	0.88	-2.1118	2.4777
T6	-0.5213	1.4344	-0.36	0.72	-3.3327	2.2900
San Francisco	0.0233	0.8095	0.03	0.98	-1.5633	1.6098
Detroit	0.2148	0.5208	0.41	0.68	-0.8059	1.2355
Hawaii	0.5699	0.7064	0.81	0.42	-0.8146	1.9544
Iowa	0.4737	0.6031	0.79	0.43	-0.7084	1.6559
Seattle	-0.6614	1.1196	-0.59	0.56	-2.8558	1.5329
Utah	0.3222	1.0210	0.32	0.75	-1.6789	2.3233
Atlanta	-0.4710	1.0412	-0.45	0.65	-2.5117	1.5698
San Jose	0.1575	1.0719	0.15	0.88	-1.9434	2.2584
Los Angeles	0.3037	0.5653	0.54	0.59	-0.8043	1.4116
Age 70-74	0.8014	0.3895	2.06	0.04	0.0381	1.5648
Age 75-79	0.3876	0.5916	0.66	0.51	-0.7719	1.5471
Age 80+	-0.3236	1.0375	-0.31	0.76	-2.3570	1.7099
marital	1.2293	0.4620	2.66	0.01	0.3238	2.1349
constant	-5.8179	1.0908	-5.33	0.00	-7.9559	-3.6798

Table 3-7 – continued. Coefficient Estimates from Semiparametric Outcomes Model with Indicators for Each Time Period.

	Coefficient	Standard Error	z	P>|z|	Confidence Interval	
Mastectomy						
T1	1.4685	1.0360	1.42	0.16	-0.5621	3.4990
T2	1.2809	1.0442	1.23	0.22	-0.7657	3.3275
T3	-0.3313	1.2325	-0.27	0.79	-2.7470	2.0844
T4	0.5819	1.1203	0.52	0.60	-1.6139	2.7777
T5	-0.5139	1.4148	-0.36	0.72	-3.2869	2.2590
T6	-0.2005	1.4127	-0.14	0.89	-2.9693	2.5683
San Francisco	0.2763	0.8726	0.32	0.75	-1.4340	1.9866
Detroit	1.0487	0.5962	1.76	0.08	-0.1199	2.2172
Hawaii	0.2552	1.1313	0.23	0.82	-1.9621	2.4725
Iowa	0.2612	0.6734	0.39	0.70	-1.0585	1.5810
Seattle	0.0038	0.8711	0.00	1.00	-1.7034	1.7111
Utah	0.3396	1.1331	0.30	0.76	-1.8812	2.5604
Atlanta	0.8356	0.7112	1.18	0.24	-0.5582	2.2295
San Jose	-0.0517	1.1212	-0.05	0.96	-2.2492	2.1458
Los Angeles	0.4805	0.7069	0.68	0.50	-0.9051	1.8661
constant	-5.9499	1.0671	-5.58	0.00	-8.0414	-3.8583

Bold indicates significance at the 10% level. Standard errors adjusted for clustering on identification number.

Table 3-8. Coefficient Estimates from Semiparametric Outcomes Model with Parametric Duration.

	Coefficient	Standard Error	z	P>|z|	Confidence Interval	
BCS Only						
tau	-0.3600	0.0721	-4.99	0.0000	-0.5013	-0.2187
San Francisco	0.2280	0.4087	0.56	0.5770	-0.5731	1.0292
Detroit	-0.0970	0.4130	-0.23	0.8140	-0.9066	0.7125
Hawaii	-0.6152	1.0754	-0.57	0.5670	-2.7229	1.4925
Iowa	0.4621	0.4144	1.12	0.2650	-0.3501	1.2743
New Mexico	0.6551	0.6078	1.08	0.2810	-0.5361	1.8463
Seattle	0.3438	0.4299	0.80	0.4240	-0.4988	1.1864
Utah	0.8553	0.5502	1.55	0.1200	-0.2230	1.9337
Georgia	0.3863	0.5015	0.77	0.4410	-0.5967	1.3693
San Jose	0.9048	0.4550	1.99	0.0470	0.0131	1.7965
Los Angeles	0.2286	0.3880	0.59	0.5560	-0.5318	0.9890
Age 70-74	-0.2426	0.2593	-0.94	0.3500	-0.7508	0.2657
Age 75-79	-0.1999	0.2745	-0.73	0.4660	-0.7378	0.3381
Age 80+	-0.4883	0.3188	-1.53	0.1260	-1.1131	0.1366
marital	0.2896	0.2069	1.40	0.1620	-0.1159	0.6950
constant	-2.6943	0.3890	-6.93	0.0000	-3.4567	-1.9318
BCS with Radiation						
tau	-0.1039	0.1064	-0.98	0.3290	-0.3124	0.1046
San Francisco	0.0138	0.8033	0.02	0.9860	-1.5606	1.5883
Detroit	0.2093	0.5196	0.40	0.6870	-0.8091	1.2277
Hawaii	0.5651	0.7066	0.80	0.4240	-0.8198	1.9500
Iowa	0.4572	0.6008	0.76	0.4470	-0.7203	1.6347
Seattle	-0.6583	1.1226	-0.59	0.5580	-2.8585	1.5419
Utah	0.3500	1.0285	0.34	0.7340	-1.6657	2.3658
Atlanta	-0.4639	1.0459	-0.44	0.6570	-2.5138	1.5861
San Jose	0.1562	1.0457	0.15	0.8810	-1.8933	2.2057
Los Angeles	0.3055	0.5658	0.54	0.5890	-0.8034	1.4144
Age 70-74	0.7986	0.3904	2.05	0.0410	0.0334	1.5637
Age 75-79	0.3899	0.5926	0.66	0.5110	-0.7716	1.5515
Age 80+	-0.3199	1.0345	-0.31	0.7570	-2.3475	1.7076
marital status	1.2274	0.4617	2.66	0.0080	0.3224	2.1323
constant	-5.2528	0.5770	-9.10	0.0000	-6.3837	-4.1220
Mastectomy						
tau	-0.3763	0.1321	-2.85	0.0040	-0.6353	-0.1174
San Francisco	0.2742	0.8718	0.31	0.7530	-1.4345	1.9829
Detroit	1.0474	0.5954	1.76	0.0790	-0.1197	2.2144
Hawaii	0.2548	1.1301	0.23	0.8220	-1.9601	2.4696
Iowa	0.2602	0.6732	0.39	0.6990	-1.0592	1.5796
Seattle	0.0009	0.8704	0.00	0.9990	-1.7051	1.7069
Utah	0.3544	1.1344	0.31	0.7550	-1.8689	2.5778
Atlanta	0.8383	0.7126	1.18	0.2390	-0.5584	2.2349
San Jose	-0.0435	1.1223	-0.04	0.9690	-2.2432	2.1562
Los Angeles	0.4781	0.7074	0.68	0.4990	-0.9083	1.8645
constant	-4.1279	0.5895	-7.00	0.0000	-5.2832	-2.9726

Bold indicates significance at the 10% level. Standard errors adjusted for clustering on identification number.

Table 3-9. Predicted Proportion of Subsequent Breast Events and of Disease-free Survival from Period-to-Period, Conditional on Having No Subsequent Breast Event in Prior Period and Based on Mean Values of Covariates.

	BCS	BCS with Radiotherapy	Mastectomy
Semiparametric model with T1-T7 duration variables			
Hazard rates			
Period 1	0.0537	0.0117	0.0159
2	0.0366	0.0086	0.0132
3	0.0259	0.0141	0.0027
4	0.0215	0.0059	0.0066
5	0.0188	0.0090	0.0022
6	0.0029*	0.0045	0.0030
7	0.0029*	0.0075	0.0037
Disease-free survival			
Period 1	0.9463	0.9883	0.9841
2	0.9116	0.9798	0.9711
3	0.8880	0.9660	0.9685
4	0.8689	0.9603	0.9621
5	0.8526	0.9516	0.9600
6	0.8501	0.9474	0.9570
7	0.8477	0.9402	0.9535
Semiparametric model with parametric tau			
Hazard rates			
Period 1	0.0534	0.0118	0.0155
2	0.0379	0.0107	0.0107
3	0.0267	0.0096	0.0074
4	0.0188	0.0087	0.0051
5	0.0132	0.0078	0.0035
6	0.0092	0.0071	0.0024
7	0.0065	0.0064	0.0016
Disease-free survival			
Period 1	0.9466	0.9882	0.9845
2	0.9107	0.9776	0.9739
3	0.8864	0.9682	0.9667
4	0.8697	0.9598	0.9618
5	0.8582	0.9522	0.9584
6	0.8503	0.9455	0.9561
7	0.8448	0.9395	0.9546

Note: Multiply by 100 for percentages. See Figures 3-1 through 3-4 for graphical representation.

*Too few exits in periods 6 and 7 following BCS Alone, so last two periods were combined.

Figure 3-2. Probability of Subsequent Breast Event
Semiparametric Model with Duration Indicator Variables

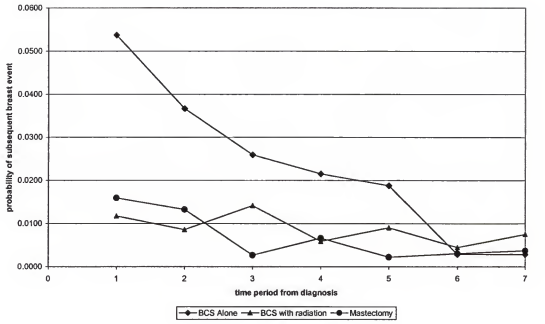


Figure 3-3. Disease-free Survival Semiparametric Model with Duration Indicator Variables

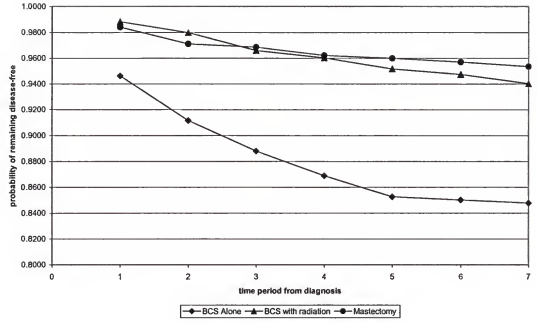


Figure 3-4. Probability of Subsequent Breast Event
Semiparametric Model with Single Duration Variable

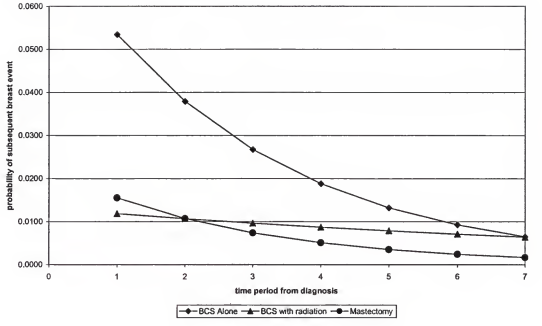


Figure 3-5. Disease-free Survival
Semiparametric Model with Single Duration Variable

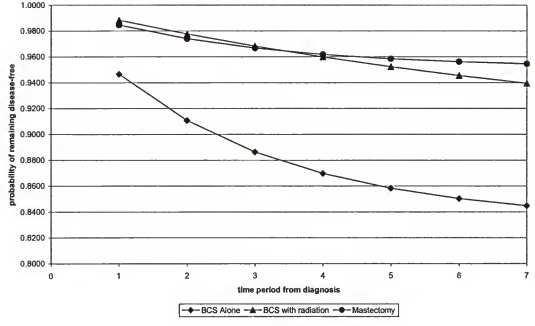


Table 3-10. Differences in Survival Curves, Based on Outcomes Model with Parametric Duration and a Standardized Population, Bootstrapped 100 Times.

Difference in Disease-free Survival over 7 Years	Observed Value	Standard Error	Confidence Interval	
BCS - BCS with radiation	-0.5693	0.2272	-1.0201	-0.1185
BCS - Mastectomy	-0.7068	0.2401	-1.1832	-0.2304
BCS with radiation - Mastectomy	-0.1376	0.1295	-0.3946	0.1194

Note: Survival functions are calculated for a hypothetical married woman in the Connecticut registry, age 65-69.

Chapter 4

Discussion

Treatment Outcomes

This study demonstrates that there are substantial differences in rates of subsequent breast events following treatment of ductal carcinoma in situ (DCIS) by BCS alone, BCS with radiotherapy, or mastectomy. The average unadjusted rates of subsequent breast events by treatment for all 7 years of data show that mastectomy has the lowest rate (4%), followed by BCS with radiotherapy (6%) and BCS alone (13%). There are variables in the model that can help explain some of this variation, including indicators for registry, age, and marital status categories. Many other variables were in the original form of the model, including poverty level, rural, and race, but after testing for their significance and determining their impact on outcomes, a more parsimonious model was implemented.

The semiparametric model allows for estimation of rates of subsequent breast events and disease-free survival with controls for covariates. The probability of a subsequent breast event at the end of period 1, 18 months after diagnosis, was 5% for BCS and approximately 1% for mastectomy or BCS with radiotherapy. By the end of period 7, 7.5 years after diagnosis, the accumulated probability is about 5% for mastectomy, 6% for BCS with radiotherapy, and 15% for BCS alone. Disease-free survival after 7 periods, or 7.5 years after diagnosis, was 95% for mastectomy, 94% for BCS with radiotherapy, and 85% for BCS alone. The prior expectation was that BCS with radiation would prove better than BCS alone given clinical trial results.

The findings suggest that breast events following BCS with radiotherapy occur with about the same probability as mastectomy. Whether these events are DCIS or invasive breast cancer – and if the proportion of these vary by treatment type – is unknown because the data conflict on subsequent diagnoses.

After 5 years of follow-up in the National Surgical Adjuvant Breast and Bowel Project trial B-17 comparing lumpectomy (i.e., BCS alone) to BCS with radiation for treatment of DCIS the investigators showed that women undergoing BCS alone had worse event-free survival (74%) compared to BCS with radiation (84%) (12), a similar trend to the results presented here. Additional follow-up data from the B-17 trial also substantiated the added benefit of radiation with BCS (13). Breast events were more broadly defined in the B-17 trial – including a positive tumor at a local, regional, or distant site, presence of ipsilateral or contralateral breast cancer, regional or distant metastasis or a second primary tumor other than a breast tumor occurring after the initial operation – than in the present study, so that accounts for at least some of the difference in disease-free survival rates.

Because the data are not from a randomized controlled trial, there is no basis for statistical equivalence across treatment groups. In fact, it is likely that women undergoing mastectomy had more complex or severe disease. Thus, all else equal, women undergoing mastectomy would be expected to have worse outcomes. The overwhelming results of longer disease-free survival for women treated by mastectomy and BCS with radiotherapy found in the present study of older women goes against the anticipated bias. As found in one observational, non-population-

based study, tumors of smaller size and lower grade were associated with higher rates of BCS, and only 45% of BCS patients received radiotherapy (42), providing evidence of the potential selection bias in this study. Even though there might be selection bias, the direction of the bias – that women undergoing more involved treatment should fare worse – makes the conclusions drawn here stronger because these women actually do better. No factors biasing the results in the opposite direction have been identified by this author.

Many of the demographic covariates in the outcomes models – that is, the models with nonparametric or parametric duration variables – were statistically insignificant and had minimal, if any, association with the outcome studied. Therefore, the variables were dropped even though they were shown to be important in other studies. The dropped variables include race, poverty level, degree rural, and educational attainment. Because these variables, except for race, were taken from the zip-code level rather than individual level, there is measurement error which adds to the imprecision of their estimation and subsequent statistical insignificance. The variables were much more important in the initial treatment choice rather than in predicting the probability of subsequent breast events.

Three registries had a significant association with worse outcomes. Women treated by BCS alone in the Los Angeles metropolitan registry were more likely to succumb to subsequent breast events, as were women treated by BCS with radiotherapy in the San Francisco area, and women treated with mastectomy in the Detroit registry, all else equal.

Age also was associated with worse outcomes for women undergoing BCS with radiotherapy. The younger and oldest age groups for the nonparametric duration and parametric duration models, respectively, had higher expected rates of subsequent breast events.

The analysis of treatment by mastectomy only over an extended period indicated that the low hazard rates found in a shorter time period extends to 12 years. (See Appendix B.) This trend is statistically significant and gives hope to women diagnosed and treated by mastectomy for DCIS that their chances of a recurrence of DCIS or subsequent invasive breast cancer are low, once they make it beyond about period 4, or 4.5 years after diagnosis. The disease-free survival rates and hazard rates are nearly identical to the estimates obtained in the primary outcomes analysis over the period 1991-1998, supporting those findings.

If disease-free survival were the sole factor in the choice of treatment for DCIS, then the decision would be clear to either undergo mastectomy or BCS with radiotherapy. In fact, it is not absolutely clear that BCS alone is a mistake, because women receiving radiation in their initial treatment cannot later undergo radiation should they have an ipsilateral recurrence or subsequent invasive breast cancer. At that point, their clinical options would be limited to mastectomy because the site could not be irradiated twice. Some surgeons might urge patients to "save" the option of radiation for future potential cancer treatment. The trend towards use of BCS and away from mastectomy seems disturbing, but when overall survival is part

of the decision-making process some women and physicians may want to be able to use radiation treatment later if necessary.

Other factors influencing treatment could be that patients choosing to undergo BCS alone may have wanted the cosmetic results associated with breast preservation but did not want to undergo weeks of radiation therapy. Another possibility is that patients intended to receive radiotherapy but could not get to the treatment site, whether for reasons of transportation, family obligations, or the like. Another reason for the trend could be that surgeons believed they were getting clear margins and therefore did not need to refer patients for radiation.

The significant result presented here that mastectomy or BCS with radiotherapy has a considerably higher disease-free survival rate, and that this trend goes against the expected biases, only adds to the robustness of the findings and makes the recommendation against the widespread use of BCS alone even stronger. In the initial treatment decision, the trade-offs of breast preservation or possible health consequences of radiotherapy must also be weighed. But based only on the high probability of subsequent breast events after BCS alone, this treatment strategy should be avoided for DCIS except for certain subgroups that might not need radiation, such as women diagnosed with small tumors and no comedo necrosis. Women and their physicians must at minimum discuss all treatment options and their benefits and consequences.

Variations in Treatment Choice

This study also identified significant differences in treatment rates for DCIS across SEER registries. Even after controlling for multiple covariates, the variability in the treatment rates did not decrease. Other factors also matter in treatment choice, including year of diagnosis, as seen by the temporal trends in treatment choice, marital status, age, percentage rural population at the zip-code level, number of radiation oncologists in the population, and educational attainment.

The high variability in treatment probabilities represented by the large sample standard deviation of each treatment across regions did not change after adjusting for the additional socioeconomic and demographic variables in the model even though certain variables independently explain treatment choice. Adding the covariates created additional noise rather than explaining the variation in rates. The variability could be due to some residual variation caused by population differences or disease prevalence characteristics.

The registry fixed effects are statistically significant in explaining variation in treatment choice, which suggests there is meaningful variation based on geographic region. These findings are similar to other studies that found geographic variations in treatment for invasive breast cancer (29,30) and DCIS (5).

Researchers also have shown that age is an important factor in determining treatment choice for invasive disease (25,29,34-36). In this analysis, increasing age was associated with a higher probability of undergoing BCS alone and a lower probability of undergoing BCS with radiotherapy. This could be due to logistical or physical difficulties of getting older women to radiation treatment 5 days a week for

6 weeks. The initial hypothesis was that older age would be associated with a higher probability of BCS alone or mastectomy, but its impact is not significant for mastectomy.

Socioeconomic factors also have been associated with use of different treatments for invasive breast cancer among Medicare beneficiaries. Lower income and higher poverty have predicted lower use of BCS alone and increased use of mastectomy for early invasive breast cancer (37). This present study confirms that lower educational attainment in a zip-code area predicts much higher rates of mastectomy over the other treatments for DCIS, but poverty level is not as helpful in explaining treatment choice.

Race has been shown to have varying effects on treatment choice, with black women tending to have higher rates of mastectomy and "other" races having higher use of BCS with radiotherapy or mastectomy (34,42). This study showed a significant increased use of mastectomy for "other" races or ethnicities and a trend towards higher rates of BCS with radiotherapy and lower rates of BCS alone. The original study hypothesis was that non-whites would tend towards mastectomy and other races towards BCS alone because previous studies had shown this association for invasive breast cancer and DCIS (34,42). This study's findings shed light on an important question in cancer care by showing that women get different treatments by race even after controlling for many covariates.

Investigators have studied the effects of living in a rural area on receipt of treatment, with the expectation that being far from more-populated areas would

make it difficult to obtain radiotherapy. This hypothesis was supported by two studies of invasive breast cancer (70,71), and now is confirmed by this work on treatment choice for DCIS. The more rural the area, the higher the probability of receipt of mastectomy. This likely is due to the difficulties associated with accessing health care services. Not only would obtaining radiation services be burdensome if one lived a good distance from a radiation clinic, but follow-up and surveillance could be problematic in areas where seeking medical care involves extensive time and transportation costs. Mastectomy could be viewed as the treatment requiring the least follow-up.

Marital status was also significant in predicting treatment choice, with married women more likely to undergo BCS with radiotherapy but less likely to undergo BCS alone. This could be due to their expectations of spousal support throughout the radiation treatment process. The hypothesis was that marital status would be associated with higher rates of BCS with radiotherapy, because of spousal support, and mastectomy, due to less focus on body image because the women already have partners. Mastectomy rates, however, are close to the reference case.

This research finds that the number of radiation oncologists in an area influences treatment choice, which is consistent with an earlier study showing that this variable was associated with choice of BCS for early invasive breast cancer (32). Women surgically treated for DCIS often get a radiotherapy referral from the surgeon. If the surgeon knows that multiple radiation oncologists are available in the area, the surgeon probably is more likely to refer for these services. Or, perhaps more

radiation oncologists are in the area because surgeons' local practice is to refer for radiation treatment. An interesting result is also that the number of radiation oncologists in an area predicted proportionally higher rates of both BCS treatment modalities and lower use of mastectomy.

The implication of geographic variation in treatment is that some regions' patients are not receiving optimal treatment, especially where rates of BCS alone are higher. Across different regions, community norms may affect physicians' behavior (116) because physicians practice as their colleagues do and learn from the local experience with different treatment options. The treatment trends for DCIS have mirrored those for early invasive breast cancer, with an increasing use of breast-conserving surgery over time (5,29), from 33% of women in 1991 to 41% in 1996.

The estimation of variability over time suggests that the sample standard deviations are increasing during the study period with a slight decrease in the standard deviations in the last period for the two BCS modalities. This implies that during the study period there is increasing uncertainty, and therefore increasing variability, in treatment choice until the last time period.

Data Limitations

Every study has its limitations, and this one is no exception. The limitations of linked SEER-Medicare data and Census data are explored here, including their generalizability and validity.

This study only evaluated treatment for women ages 65 and over in the linked SEER-Medicare database. The database does not include histopathologic features of the DCIS lesion(s), nor does it include women under age 65. This makes generalizability to a younger population difficult, especially because younger women may present with different types of tumors than older women.

Additional information about the DCIS lesion that might aid in explaining treatment choice or the probability of subsequent breast events is unavailable in the linked SEER-Medicare data. Lesions can be classified based on appearance, growth pattern, and cytology. Pathologists often characterize DCIS by nuclear grade, amount and type of necrosis, growth and differentiation, tumor size, and architecture (117). Clinical studies have shown that risk factors for recurrence include younger age, symptomatic presentation of DCIS (i.e., not just mammographic detection), solid and cribiform architecture, comedo necrosis, involved margins, and local excision alone (117,118). However, only age and surgery type are accounted for in this analysis, so selection bias likely is still present because one cannot identify if the lesion is larger, faster growing, or of certain architectural structure which yields a higher probability of mastectomy and subsequent breast events.

The SEER data represent only 10% of the US population from 1986-1991 and 14% of the population from 1992-1996 (119). The counties that comprise the SEER registries tend to be more urban, more educated, less unemployed, and wealthier than the rest of the US population (120). By controlling for some of the socioeconomic factors with proxy variables from the 1990 Census, as is done in this

study, the results may be more generalizable to the United States population as a whole.

The linked SEER-Medicare data include persons identified in the SEER database who could be matched to Medicare enrollment files. Of these, 93% of persons ages 65 years or older in the SEER database were matched to Medicare claims files (81). It is uncertain whether the remaining 7% are different in some way from the 93% who matched or if breast cancer cases tended to match at a higher or lower rate than 93%.

There is some discordance in the treatment information contained in the Medicare and the SEER data. However, there is no true gold standard for treatment or recurrence in these data because SEER and Medicare do not overlap completely. In this study, however, Medicare is taken as the gold standard so that 6 months of treatment claims can be analyzed to determine the most extensive surgery undergone. Other recent studies have found discordance across SEER and Medicare for breast cancer treatment, but concordance there is more than 90% concordance (83,84). Analysis of the three-treatment analytic sample used in this study shows that of those with mastectomy according to Medicare, 91% were confirmed by SEER, and of those with BCS according to Medicare, 96.6% were confirmed by SEER. Of those with radiation treatment according to Medicare, 91% were confirmed by SEER.

Because Medicare claims are administrative data, they have shortcomings for the purpose of correctly identifying a recurrence of DCIS or subsequent invasive

breast cancer. First, it is impossible to separate DCIS diagnoses from breast-cancer diagnoses because the ICD-9 codes often are inconsistent by claims source. Claims for the same procedure may be coded with different ICD-9 codes across physician and inpatient claims, for example, so there is uncertainty about whether the cancer is invasive or not. Second, there is no way to identify if a subsequent diagnosis is ipsilateral or contralateral to the initial diagnosis, because laterality information is only in SEER for primary cancers but subsequent breast events are taken from Medicare claims. Third, it is impossible to identify the difference between a second primary breast cancer and a related recurrence of DCIS or invasive breast cancer in the Medicare claims. Finally, by creating a 6-month window for treatment, the sample may miss early subsequent breast events and consider them as part of the initial treatment, rather than treatment for the successive breast event. These are all limitations that could misclassify subsequent breast events. Regardless, any recurrent DCIS or subsequent invasive breast cancer is counted as a subsequent breast event, and the types are not separated.

In tallying deaths due to breast cancer in the SEER data for the purposes of ascertaining if metastatic disease were present but not found in Medicare claims, one must consider that SEER uses state death certificates to classify cause of death. A misclassification could occur, for example, if the true cause of death is breast cancer but the primary cancer stated as the cause of death is labeled as a different site. This could lead to an underestimate of the number of breast events if these persons had not experienced a subsequent breast event prior to death. However, in this study

death from breast cancer was rare and so this limitation probably has little bearing on the results.

Model Limitations

The outcomes models also have their limitations. The type of model used can only describe outcomes, but does not necessarily explain the cause-and-effect relationship of treatment and outcomes. Considering the striking effect of BCS with radiotherapy or mastectomy in reducing subsequent breast events, however, and that this effect goes against all biases, the results seem quite robust.

The semiparametric model with a fully-nonparametric baseline hazard may not be modeling endogenous treatment choice correctly. If the model were incorrect, then the mastectomy arm would be penalized towards worse outcomes, all things equal. Mastectomy outcomes rank the best with BCS and radiotherapy, however. Because endogeneity may not be modeled in an ideal way, the point estimates for disease-free survival rates and probability of subsequent breast events may be biased.

The models use registry fixed effects which may not be adequate in reducing unobserved factors that are constant within region. Unfortunately, the parametric models that can explicitly incorporate frailty, or unobserved heterogeneity, were too sensitive to assumptions about the underlying distribution and in many cases would not converge. Without incorporating a frailty distribution in the model, there still could be unobserved factors influencing treatment choice and outcomes that affect the point estimates of the models presented here. A disadvantage of frailty models,

however, is that one would have to make assumptions about the frailty distribution and its interpretation.

Areas for Future Work

To enhance the understanding of the relationship between treatment choice and outcomes for DCIS, it would be helpful to implement other methods to account for unobserved heterogeneity and selection bias. Such methods could include an instrumental variables analysis if an appropriate instrument could be identified and other parametric models that better account for unobserved factors affecting both treatment choice and outcomes. A continuous-time duration model that does this uses a parametric distribution for the underlying duration intensity with nonparametric points of support for unobserved heterogeneity, as implemented by Hamilton and Hamilton (121), based on the work of Heckman and Singer (122).

By including detailed information about the lesion – such as its size and histopathologic features – in future studies, the unobserved factors that may be influencing treatment choice and outcomes can be controlled in the model. The impact of each treatment modality may then be better described and optimal treatments can be chosen based on tumor characteristics. Clinical trials of BCS alone are now underway and may help in future decision making for DCIS treatment.

More recent approaches to management of DCIS also should be incorporated into future outcomes analyses, including tamoxifen in combination with BCS and radiotherapy. This combination therapy has been shown to reduce the probability of

subsequent invasive breast cancer in a randomized controlled trial of women diagnosed with DCIS (123).

Finally, incorporating cost, utilization, and utility data into a cost-effectiveness analysis would be helpful to inform treatment decisions for DCIS. Utility elicitation can provide information about the valuation of health states and risk aversion. If the value of breast preservation and not seeking radiotherapy makes up for the higher rates of subsequent breast events, then women may want to choose that treatment strategy. By performing a formal cost-effectiveness analysis, decision makers could see what the optimal treatment or treatments are, given patient preferences and costs.

Conclusion

This study attempted to explain variations in treatment for DCIS and identify which treatment or treatments were the best in terms of disease-free survival. Indeed there is significant variability in treatment rates across geographic regions represented by the SEER program. And even with the method's limitations, it appears that disease-free survival in the first 7 years after diagnosis is much higher after BCS with radiotherapy or mastectomy than after BCS alone.

Regions with the highest rates of BCS alone, including the San Francisco and Los Angeles metropolitan areas (57% and 47%, respectively), may not be providing the best care for women diagnosed with DCIS. All registry areas, however, have some use of BCS alone, from 21% in Hawaii and 23% in New Mexico to

California's rates which are over 40%. A total of 1,044 women (39%) diagnosed and treated from 1991-1996 in this sample from the SEER regions underwent BCS alone.

Any suboptimal treatment choice creates welfare loss because some patients are losing the benefits of better treatment. This study showed that women living in certain regions and who have certain demographic characteristics – non-white race or older age, impoverished or married – are undergoing treatment that yields worse outcomes.

There may be highly-selected patients who can benefit equally as well from BCS alone as from the other two treatments, and clinical trials are underway to determine if this is the case. But, given the results of this study, BCS alone should not be performed on women diagnosed with DCIS unless they are aware of the risk of subsequent breast events and have had the opportunity to weigh the benefits and consequences of either not undergoing radiotherapy after BCS or a mastectomy in the first place.

References

1. Sakorafas GH, Tsiotou AGH. Ductal carcinoma in situ (DCIS) of the breast: evolving perspectives. Cancer Treatment Reviews 2000;26:103-25.

2. Fonseca R, Hartmann L, Petersen IA, Donohue JH, Crotty TB, Gisvold JJ. Ductal carcinoma in situ of the breast. Annals of Internal Medicine 1997;127(1):1013-22.

3. Morrow M, Schnitt SJ, Harris JR. Harris JR, editors. Diseases of the Breast. 2 ed. Philadelphia: Lippincott Williams and Wilkins. 2000; Chapter 27, Ductal carcinoma in situ and microinvasive carcinoma. pp. 383-401.

4. Ernster V, Barclay J, Kerlikowske K, Wilkie H, Ballard-Barbash R. Mortality among women with ductal carcinoma in situ of the breast in the population-based Surveillance, Epidemiology and End Results Program. Archives of Internal Medicine 2000;160:953-8.

5. Ernster VL, Barclay J, Kerlikowske K, Grady D, Henderson IC. Incidence of and treatment for ductal carcinoma in situ of the breast. JAMA 1996;275(12):913-8.

6. American, Cancer Society. Who gets breast cancer? http://www.cancer.org/statistics/99bcff/who.html . 1999. American Cancer Society, Surveillance Research. Accessed 8-21-2000.

7. Kerlikowske K, Barclay J, Grady D, Sickles EA, Ernster V. Comparison of risk factors for ductal carcinoma in situ and invasive breast cancer. Journal of the National Cancer Institute 1997;89(1):76-82.

8. Morrow M, Schnitt SJ. Treatment selection in ductal carcinoma in situ. JAMA 2000;283(4):453-5.

9. Silverstein MJ, Poller DN, Waisman JR, Colburn WJ, Barth A, Gierson ED, Lewinsky B, Gamagami P, Slamon DJ. Prognostic classification of breast ductal carcinoma-in-situ. Lancet 1995;345(8958):1154-7.

10. Boyages J, Delaney G, Taylor R. Predictors of local recurrence after treatment of ductal carcinoma in situ: a meta-analysis. Cancer 1999;85:616-28.

11. Welch HG, Black WC. Using autopsy series to estimate the disease "reservoir" for ductal carcinoma in situ of the breast: how much more breast cancer can we find? Annals of Internal Medicine 1997;127(11):1023-8.

12. Fisher B, Costantino J, Redmond C, Fisher ER, Margolese R, Dimitrov N, Wolmark N, Wickerham DL, Deutsch M, Ore L, et al. Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. New England Journal of Medicine 1993;328(22):1581-6.

13. Fisher B, Dignam J, Wolmark N, Mamounas E, Costantino J, Poller W, Fisher ER, Wickerham DL, Deutsch M, Margolese R, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. Journal of Clinical Oncology 1998;16(2):441-52.

14. Fisher B. Highlights from recent National Surgical Adjuvant Breast and Bowl Project studies in the treatment and prevention of breast cancer. Ca: A Cancer Journal for Clinicians 1999;49:159-77.

15. Julien JP, Bijker N, Fentiman IS, Peterse JL, Delledonne V, Rouanet P, Avril A, Sylvester R, Mignolet F, Bartelink H, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. Lancet 2000;355(9203):528-33.

16. Wennberg JE, Gittelsohn A. Small area variations in health care delivery. Science 1973;182:1102-7.

17. Ganz PA, Schag CAC, Lee JJ, Polinsky ML, Tan S. Breast conservation versus mastectomy:Is there a difference in psychological adjustment or quality of life in the year after surgery? Cancer 1992;69(7):1729-38.

18. Holmberg L, Omne-Ponten M, Burns T, Adami HO, Bergstrom R. Psychosocial adjustment after mastectomy and breast-conserving treatment. Cancer 1989;64(4):969-74.

19. Fallowfield LJ. Assessment of quality of life in breast cancer. Acta Oncologica 1995;34(5):689-94.

20. National, Institutes of Health. Treatment of early-stage breast cancer. NIH Consensus Statement 8(6), 1-19. http://www.nci.nih.gov. Accessed 6-18-1990.

21. Kraft RB. The breast cancer controversy and its implications for the informed consent doctrine. Journal of Legal Medicine 1980;2(1):47-84.

22. Lerner BH. The Breast Cancer Wars: Hope, Fear, and the Pursuit of a Cure in Twentieth-Century America. New York: Oxford University Press; 2001.

23. Kleinman JC, Machlin SR, Madans J, Makuc D, Feldman JJ. Changing practice of surgical treatment of breast cancer: a national perspective. Medical Care 1983;21(12):1232-42.

24. Fisher B, Anderson S, Redmond C, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. New England Journal of Medicine 1995;333(22):1456-61.

25. Swanson GM, Satariano ER, Satariano WA, Osuch JR. Trends in conserving treatment of invasive carcinoma of the breast in females. Surgery, Gynecology and Obstetrics 1990;171:465-71.

26. Linden-Ward B; Green CH. Changing the Future: American Women in the 1960s. New York: Twayne Publishers; 1993.

27. Lazovich A, White E, Thomas DB, Moe RE. Underutilization of breast-conserving surgery and radiation therapy among women with stage I or II breast cancer. JAMA 1991;266(24):3433-8.

28. Albain KS, Green SR, Lichter AS, Hutchins LF, Wood WC, Henderson IC, Ingle JN, O'Sullivan J, Osborne CK, Martino S. Influence of patient characteristics, socioeconomic factors, geography, and systemic risk on the use of breast-sparing treatment in women enrolled in adjuvant breast cancer studies: an analysis of two intergroup trials. Journal of Clinical Oncology 1996;14(11):3009-17.

29. Farrow DC, Hunt WC, Samet JM. Geographic variation in the treatment of localized breast cancer. New England Journal of Medicine 1992;326(17):1097-101.

30. Nattinger AB, Gottlieb MS, Veum J, Yahnke D, Goodwin JS. Geographic variation in the use of breast-conserving treatment for breast cancer. New England Journal of Medicine 1992;326(17):1102-7.

31. Nattinger AB, Gottlieb MS, Hoffman RG, Walker AP, Goodwin JS. Minimal increase in use of breast-conserving surgery from 1986 to 1990. Medical Care 1996;34(5):479-89.

32. Newcomb, JL. Persistence Of Outmoded Medical Practices. 1995; Doctoral Dissertation, Washington University, St. Louis, MO.

33. Guadagnoli E, Weeks JC, Shapiro CL, Gurwitz JH, Borbas C, Soumerai SB. Use of breast-conserving surgery for treatment of stage I and stage II breast cancer. J Clin Oncol 1998;16(1):101-6.

34. Satariano ER, Swanson GM, Moll PP. Nonclinical factors associated with surgery received for treatment of early-stage breast cancer. Am J Public Health 1992;82(2):195-8.

35. Ballard-Barbash R, Potosky AL, Harlan LC, Nayfield SG, Kessler LG. Factors associated with surgical and radiation therapy for early stage breast cancer in older women. Journal of the National Cancer Institute 1996;88(11):716-26.

36. Hebert-Croteau N, Brisson J, Latreille J, Blanchette C, Deschenes L. Compliance with consensus recommendations for the treatment of early stage breast carcinoma in elderly women. Cancer 1999;85(5):1104-13.

37. Michalski TA, Nattinger AB. The influence of black race and socioeconomic status on the use of breast-conserving surgery for Medicare beneficiaries. Cancer 1997;79(2):314-9.

38. Hayman JA, Fairclough DL, Harris JR, Weeks JC. Patient preferences concerning the trade-off between the risks and benefits of routine radiation therapy after conservative surgery for early-stage breast cancer. Journal of Clinical Oncology 1997;15(3):1252-60.

39. Mandelblatt JS, Hadley J, Kerner JF, Schulman KA, Gold K, Dunmore-Griffith J, Edge S, Guadagnoli E, Lynch JJ, Meropol NJ, et al. Patterns of breast carcinoma treatment in older women: patient preference and clinical and physical influences. Cancer 2000;89(3):561-73.

40. Silliman RA, Troyan SL, Guadagnoli E, Kaplan SH, Greenfield S. The impact of age, marital status, and physician-patient interactions on the care of older women with breast carcinoma. Cancer 1997;80(7):1326-34.

41. Fisher ER, Leeming R, Anderson S, Redmond C, Fisher B. Conservative management of intraductal carcinoma (DCIS) of the breast. Collaborating NSABP investigators. Journal of Surgical Oncology 1991;47(3):139-47.

42. Winchester DJ, Menck HR, Winchester DP. National treatment trends for ductal carcinoma in situ of the breast. Archives of Surgery 1997;132(6):660-5.

43. Chassin MR, Brook RH, Park RE, Keesey J, Fink A, Kosecoff J, Kahn K, Merrick N, Solomon DH. Variations in the use of medical and surgical services by the Medicare population. New England Journal of Medicine 1986;314:285-90.

44. Wennberg JE, Freeman JL, Culp WJ. Are hospital services rationed in New Haven or over-utilised in Boston? Lancet 1987;1(8543):1185-9.

45. Phelps CE, Parente ST. Priority setting in medical technology and medical practice assessment. Medical Care 1990;28(8):703-23.

46. Lu-Yao G, McLerran D, Wasson J, Wennberg JE. An assessment of radical prostatectomy: time trends, geographic variation, and outcomes. JAMA 1993;269:2633-6.

47. Wennberg JE, Freeman JL, Shelton RM, Bubolz TA. Hospital use and mortality among Medicare beneficiaries in Boston and New Haven. New England Journal of Medicine 1989;321:1168-73.

48. Cleary PD, Greenfield S, Mulley AG, Pauker SG, Schroeder SA, Wexler L, McNeil BJ. Variations in length of stay and outcomes for 6 medical and surgical conditions in Massachusetts and California. JAMA 1991;266(1):73-9.

49. Cooper GS, Yuan Z, Chak A, Rimm AA. Geographic and patient variation among Medicare beneficiaries in the use of follow-up testing after surgery for nonmetastatic colorectal carcinoma. Cancer 1999;85(10):2124-31.

50. Guadagnoli E, Hauptman PJ, Ayanian JZ, Pashos CL, McNeil BJ, Cleary PD. Variation in the use of cardiac procedures after acute myocardial infarction. New England Journal of Medicine 1995;333(9):573-8.

51. Leape LL, Park RE, Solomon DH, Chassin MR, Kosecoff J, Brook RH. Does inappropriate use explain small-area variations in the use of health care services? JAMA 1990;263(5):669-72.

52. Pilote L, Califf RM, Sapp S, Miller DP, Mark DB, Weaver WD, Gore JM, Armstrong PW, Ohman EM, Topol EJ. Regional variation across the United States in the management of acute myocardial infarction. New England Journal of Medicine 1995;333(9):565-72.

53. Gittelsohn A, Powe NR. Small area variations in health care delivery in Maryland. Health Services Research 1995;30(2):295-317.

54. Javitt JC, Kendix M, Tielsch JM, Steinwachs DM, Schein OD, Kolb MM, Steinberg EP. Geographic variation in utilization of cataract surgery. Medical Care 1995;33(1):90-105.

55. Diehr P, Cain K, Ye Z, Abdul-Salam F. Small area variation analysis: methods for comparing several diagnosis-related groups. Medical Care 1993;31(5Supp):YS45-YS53.

56. Griliches Z. Hybrid corn: an exploration in the economics of technological change. Econometrica 1957;25:501-22.

57. Griliches Z. Hybrid corn and the economics of innovation. Science 1960;132:275-80.

58. Hu, T. Essays on cardiologists' behavior: medical variations, impact of PSROs and response to PPS 1996; Doctoral Dissertation, University of Rochester, Rochester, NY.

59. Rogers EM. Diffusion of innovations. Fourth ed. New York: The Free Press; 1995.

60. Phelps CE. Diffusion of information in medical care. Journal of Economic Perspectives 1992;6(3):23-42.

61. Paul-Shaheen P, Clark JD, Williams D. Small area analysis: a review and analysis of the North American literature. Journal of Health Politics, Policy and Law 1987;12(4):741-809.

62. Phelps CE, Mooney C. Arnould RJ, Rich RF, White WD, editors.Competitive approaches to health care reform. Washington, DC: The Urban Institute Press; 1993; Chapter 7, Variations in medical practice use: causes and consequences. pp. 139-78.

63. Phelps CE. Welfare loss from variations: further considerations. Journal Of Health Economics 1995;14:253-60.

64. Wennberg JE. Population illness rates do not explain population hospitalization rates. A comment on Mark Blumberg's thesis that morbidity adjusters are needed to interpret small area variations. Medical Care 1987;25(4):354-9.

65. Eddy DM. Variations in physician practice: the role of uncertainty. Health Affairs 1985;5(2):74-89.

66. McPherson K, Wennberg JE, Hovind OB, Clifford P. Small-area variations in the use of common surgical procedures: an international comparison of New England, England, and Norway. New England Journal of Medicine 1982;307(21):1310-4.

67. Davis P, Gribben B, Scott A, Lay-Yee R. The "supply hypothesis" and medical practice variation in primary care: testing economic and clinical models of inter- practitioner variation. Social Science & Medicine 2000;50(3):407-18.

68. McMahon LF, Wolfe RA, Griffith JR, Cuthbertson D. Socioeconomic influence on small area hospital utilization. Medical Care 1993;31(5Supp):YS29-YS36.

69. Nattinger AB, Goodwin JS. Geographic and hospital variation in the management of older women with breast cancer. Cancer Control 1994;1(4):334-8.

70. Athas WF, Adams-Cameron M, Hunt WC, Amir-Fazli A, Key CR. Travel distance to radiation therapy and receipt of radiotherapy following breast-

conserving surgery. Journal of the National Cancer Institute 2000;92(3):269-71.

71. Nattinger AB, Kneusel RT, Hoffmann RG, Gilligan MA. Relationship of distance from a radiotherapy facility and initial breast cancer treatment. Journal of the National Cancer Institute 2001;93(17):1344-6.

72. Carlisle DM, Valdez RB, Shapiro MF, Brook RH. Geographic variation in rates of selected surgical procedures within Los Angeles County. Health Services Research 1995;30(1):27-42.

73. Makuc, D., Freid, V.M., and Parsons, P.E. Health insurance and cancer screening among women. Hyattsville, MD. National Center for Health Statistics. 1994; 254. p.1 Advance Data.

74. Park RE, Brook RH, Kosecoff J, Keesey J, Rubenstein L, Keeler E, Kahn KL, Rogers WH, Chassin MR. Explaining variations in hospital death rates: randomness, severity of illness, quality of care. JAMA 1990;264:484-90.

75. Diehr P, Cain K, Kreuter W, Rosenkranz S. Can small-area analysis detect variation in surgery rates? The power of small-area variation analysis. Medical Care 1992;30(6):484-502.

76. Chassin MR. Explaining geographic variations: the enthusiasm hypothesis. Medical Care 1993;31(5Supp):YS37-YS44

77. Burns RB, Freund KM, Kasten L, Feldman H, McKinlay JB. Physician characteristics: do they influence the evaluation and treatment of breast cancer in older women? American Journal of Medicine 1997;103(4):263-9.

78. Phelps CE. Greenman J, editor.Health Economics. 1 ed. New York: HarperCollins Publishers, Inc.; 1992.

79. Nattinger AB, Hoffmann RG, Shapiro R, Gottlieb MS, Goodwin JS. The effect of legislative requirements on the use of breast-conserving surgery. New England Journal of Medicine 1996;335(14):1035-40.

80. Annas GJ. Friedman E, editors.An unfinished revolution: women and health care in America. New York: United Hospital Fund of New York; 1994; Chapter: Women, health care, and the law.

81. Fahey A. Documentation for the Patient Entitlement and Diagnosis Summary File. 2000; Maryland: Information Management Systems, Inc. & Applied Research Program, National Cancer Institute.

82. Cooper GS, Yuan Z, Stange KC, Dennis LK, Amini SB, Rimm AA. Agreement of Medicare claims and tumor registry data for assessment of cancer-related treatment. Medical Care 2000;38(4):411-21.

83. Du X, Freeman JL, Warren JL, Nattinger AB, Zhang D, Goodwin JS. Accuracy and completeness of Medicare claims data for surgical treatment of breast cancer. Medical Care 2000;38(7):719-27.

84. Du X, Freeman JL, Goodwin JS. Information on radiation treatment in patients with breast cancer: the advantages of the linked Medicare and SEER data. Journal of Clinical Epidemiology 1999;52(5):463-70.

85. Anderson, R.N. United States Life Tables, 1997. Hyattsville, MD. Centers for Disease Control and Prevention, National Center for Health Statistics. 1999; v.47, no. 28. National Vital Statistics Reports.

86. Ernster VL, Barclay J, Kerlikowske K, Wilkie H, Ballard-Barbash R. Mortality among women with ductal carcinoma in situ of the breast in the population-based surveillance, epidemiology and end results program. Archives of Internal Medicine 2000;160(7):953-8.

87. International Classification of Diseases, 9th Revision. Clinical Modification, Fourth Edition ed. Los Angeles, CA: Practice Management Information Corporation; 1995.

88. Kirschner CG; Davis S; Jackson J, et al. Physicians' Current Procedural Terminology: CPT '97. Chicago, IL: American Medical Association; 1996.

89. Warren JL, Feuer E, Potosky AL, Riley GF, Lynch CF. Use of Medicare hospital and physician data to assess breast cancer incidence. Medical Care 1999;37(5):445-56.

90. Warren JL, Riley GF, McBean AM, Hakim R. Use of Medicare data to identify incident breast cancer patients. Health Care Financing Review 1996;18:237-46.

91. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. Journal of Clinical Epidemiology 2000;53:1258-67.

92. Pocock SJ, Cook DG, Beresford SAA. Regression of area mortality rates on explanatory variables: what weighting is appropriate? Applied Statistics 1981;30(3):286-95.

93. Pearson K. On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling. Philosophical Magazine 1900;5(50):157-75.

94. Conover WJ. Practical Nonparametric Statistics. 3d ed. New York: John Wiley & Sons; 1999.

95. Fienberg SE. The Analysis of Cross-Classified Categorical Data. 2d ed. Cambridge, MA: MIT Press; 1980.

96. Hosmer DW; Lemeshow S. Applied Logistic Regression. 2d ed. New York: John Wiley & Sons, Inc.; 2000.

97. Maddala GS. Deaton A, McFadden D, and Sonnenschein H, editors.Limited-Dependent and Qualitative Variables in Econometrics. Cambridge, UK: Cambridge University Press; 1983.

98. Chatterjee S; Hadi AS; Price B. Regression Analysis by Example. 3d ed. New York: John Wiley & Sons.; 2000.

99. Hausman J, McFadden D. Specification tests in econometrics. Econometrica 1984;52:1219-40.

100. Mooney, C.Z. and Duval, R.D. Bootstrapping: A Nonparametric Approach to Statistical Inference. Newbury Park, California: Sage Publications. 1993; 07-095. Quantitative Applications in the Social Sciences.

101. Osteen RT, Steele GDJ, Menck HR, Winchester DP. Regional differences in surgical management of breast cancer. Ca: A Cancer Journal for Clinicians 1992;42(1):39-43.

102. Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 2001;285(7):885-92.

103. Hayman JA, Hillner BE, Harris JR, Pierce LJ, Weeks JC. Cost-effectiveness of adding an electron-beam boost to tangential radiation therapy in patients with negative margins after conservative surgery for early-stage breast cancer. Journal of Clinical Oncology 2000;18(2):287-95.

104. Greenfield S. The state of outcome research: are we on target? New England Journal of Medicine 1989;320(17):1142-3.

105. Wennberg JE, Mulley AGJ, Hanley D, Timothy RP, Jr FJ, Roos NP, Barry MJ, McPherson K, Greenberg ER, Soule D. An assessment of prostatectomy for benign urinary tract obstruction. Geographic variations and the evaluation of medical care outcomes. JAMA 1988;259(20):3027-30.

106. Wennberg JE, Roos N, Sola L, Schori A, Jaffe R. Use of claims data systems to evaluate health care outcomes. Mortality and reoperation following prostatectomy. JAMA 1987;257(7):933-6.

107. Romano PS, Roos LL, Luft HS, Jollis JG, Doliszny K. A comparison of administrative versus clinical data: coronary artery bypass surgery as an example. Ischemic Heart Disease Patient Outcomes Research Team. Journal of Clinical Epidemiology 1994;47(3):249-60.

108. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases 1987;40(5):373-83.

109. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. Journal of Clinical Epidemiology 1992;45(6):613-9.

110. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Medical Care 1998;36(1):8-27.

111. Wang PS, Walker A, Tsuang M, Orav EJ, Levin R, Avorn J. Strategies for improving comorbidity measures based on Medicare and Medicaid claims data. Journal of Clinical Epidemiology 2000;53(6):571-8.

112. Trimble EL, Carter CL, Cain D, Freidlin B, Ungerleider RS, Friedman MA. Representation of older patients in cancer treatment trials. Cancer 1994;74(7 Suppl):2208-14.

113. McLellan M, McNeil BJ, Newhouse JP. Does more intensive treatment of acute myocardial infarction in the elderly reduce mortality? Analysis using instrumental variables. JAMA 1994;272(11):859-66.

114. Huber PJ. Robust estimation of a location parameter. Annals of Mathematic Statistics 1964;35:73-101.

115. Van Zee KJ, Liberman L, Samli B, Tran KN, McCormick B, Petrek JA, Rosen PP, Borgen PI. Long term follow-up of women with ductal carcinoma in situ treated with breast-conserving surgery: the effect of age. Cancer 1999;86:1757-67.

116. McMahon LF, Wolfe RA, Tedeschi PJ. Variation in hospital admissions among small areas: a comparison of Maine and Michigan. Medical Care 1989;27(6):623-31.

117. Silverstein MJ. Ductal carcinoma in situ of the breast. British Medical Journal 1998;317:734-9.

118. Bijker N, Peterse JL, Duchateau L, Fentiman IS, Duval C, Di Palma S, Simony-Lafontaine J, de Mascarel I, van de Vijver MJ. Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in-situ: analysis of European Organization for Research and Treatment of Cancer Trial 10853. Journal of Clinical Oncology 2001;19(8):2263-71.

119. Ries, L.A., Eisner, M.P., Kosary, C.L. et al. SEER Cancer Statistics Review, 1973-1997. Bethesda, MD. National Cancer Institute. 2000.

120. Nattinger AB, McAuliffe TL, Schapira MM. Generalizability of the surveillance, epidemiology, and end results registry population: factors relevant to epidemiologic and health care research. Journal of Clinical Epidemiology 1997;50(8):939-45.

121. Hamilton BH, Hamilton VH. Estimating surgical volume - outcome relationships applying survival models: accounting for frailty and hospital fixed effects. Health Economics 1997;6:383-95.

122. Heckman J, Singer BA. A method for minimizing the impact of distributional assumptions in econometric models for duration data. Econometrica 1984;52:271-320.

123. Fisher B, Dignam J, Wolmark N, Wickerham DL, Fisher ER, Mamounas E, Smith R, Begovic M, Dimitrov N, Margolese R, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet 1999;353:1993-2000.

Appendix A

Comorbidity Indices

Klabunde et al. developed comorbidity indices using Medicare claims data from national cohorts of elderly breast cancer patients (1). They showed that the inpatient and physician claims separately explained noncancer mortality. Klabunde et al. used conditions identified in inpatient hospital claims or in physician claims only (not both) to create two separate comorbidity indices.

Some Part B (physician and outpatient claims) codes were excluded in comorbidity assessment. They excluded ICD-9-CM codes from Part B clinical laboratory, diagnostic imaging, and durable medical equipment (DME) claims to maximize the likelihood that clinicians had assigned the codes. Other Part B codes excluded in the comorbidity assessment were: 1) if a code appeared only once in physician claims during the year prior to patient's cancer diagnosis, and an identical code was not present in inpatient hospital claims, or 2) a code appeared more than once in physician claims within a 30-day period but never appeared again in either inpatient hospital or physician claims. This was due to concern over poor agreement between medical records and administrative claims.

The authors used estimated coefficient values as weights in the comorbidity indices, unlike Charlson et al. (2). (See Table A-1.) The coefficients are estimated from a Cox proportional hazards model with 2-year noncancer mortality as the

dependent variable and age and comorbid conditions identified in inpatient and physician claims as the independent variables (1).

The present study uses the same methodology as Klabunde and colleagues to calculate comorbidity indices for the treatment-choice model, as described in Chapter 2.

References

1. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. Journal of Clinical Epidemiology 2000;53:1258-67.

2. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases 1987;40(5):373-83.

Table A-1. Condition Coefficients for Comorbidities Derived from Medicare Claims Data for the Breast Cohort.

Condition	Inpatient claims coefficient	Physician/Outpatient claims coefficient
Diabetes	0.52	0.65
Chronic pulmonary disease	0.83	0.84
Congestive heart failure	0.76	0.74
Cerebrovascular disease	-0.09	1.10
Peripheral vascular disease	0.23	0.75
Paralysis	1.23	-0.08
Acute myocardial infarction	0.05	-0.99
Old myocardial infarction	1.00	--
Moderate/severe renal disease	1.34	1.20
Diabetes with complications	0.64	0.36
Ulcer disease	0.03	-0.65
Dementia	0.14	1.07
Rheumatologic disease	0.92	-0.45
Minor liver disease	1.19	1.63

Note: Taken directly from Klabunde, et al. (1)

Appendix B

Outcomes Analysis of Mastectomy Only

The sample for the analysis of outcomes for mastectomy is comprised of 1,738 women diagnosed with unilateral DCIS from 1986-1996 with 141 (8%) women experiencing subsequent breast events. The sample was taken from women diagnosed with DCIS (as seen in Table 2-1), with exclusions if women were not treated by mastectomy (n=2529) and then if they were in an HMO during the month of diagnosis or during 24 months after diagnosis (n=344).

The sample characteristics are shown in Table B-1. The mean age of diagnosis is 72 years old, with a standard deviation of 5.8; the largest age group is those ages 65-69, with 663 women or 38% of the sample. The Detroit, Michigan registry provides the greatest number of cases, with 293 (17%), followed by Iowa with 270. Eighty-six percent of the women are white. The year of diagnosis ranges from 1986 to 1996, and because more women over time were undergoing non-mastectomy treatments, more women diagnosed and treated with mastectomy occur in the earlier years of the sample, with the peak at 13% diagnosed in 1988.

Table B-1. Descriptive Statistics of Demographic Factors for Outcomes Analysis for Mastectomy Only based on Linked SEER-Medicare Database, 1986-1996 (n=1738).

	n (%)	Mean	Standard Deviation
No subsequent breast event	1597		
Subsequent breast event	141 (8)		
Age in Years		72	5.8
65-69	663 (38)		
70-74	514 (30)		
75-79	320 (18)		
80+	241 (14)		
Registry			
San Francisco	151 (9)		
Connecticut	221 (13)		
Detroit	293 (17)		
Hawaii	67 (4)		
Iowa	270 (16)		
New Mexico	94 (5)		
Seattle	175 (10)		
Utah	61 (4)		
Georgia	155 (9)		
San Jose	86 (5)		
Los Angeles	165 (9)		
Race/Ethnicity			
White	1495 (86)		
Black	135 (8)		
Other	108 (6)		
Year of Diagnosis			
1986	113 (7)		
1987	191(11)		
1988	231 (13)		
1989	195 (11)		
1990	206 (12)		
1991	162 (9)		
1992	146 (8)		
1993	122 (7)		
1994	137 (8)		
1995	130 (7)		
1996	105 (6)		

Percentages for each variable may not add to 100% due to rounding errors.

All multivariate models for outcomes analysis of treatment by mastectomy consist of indicator variables for registries and age groups. The first model is semiparametric and includes dummy variables for each year a patient is in the data set alive without experiencing a subsequent breast event. The second model incorporates one parametric duration variable, tau, which takes on values of 1 to 7, dependent on how long the person's spell as alive without a subsequent breast event lasts. In addition, there are year-of-diagnosis indicators in the analysis.

In following outcomes of mastectomy over time, the model coefficients show that compared to being diagnosed in 1992 or 1993, being diagnosed earlier yields a significantly higher risk of succumbing to a subsequent breast event, probably in part because these women can be followed for a much longer time than someone diagnosed in 1992 or later. (See Tables B-2 and B-3.) The Detroit, Michigan, registry again has worse outcomes with an odds ratio for a subsequent breast event of 2.0 relative to the reference registry, Connecticut, all other things equal. The San Jose metropolitan area also has higher rates of subsequent breast events for mastectomy with an odds ratio of 2.5 compared to the reference group. The longer a patient remains alive without succumbing to a subsequent breast event, the higher the probability that person will not experience one. That is, staying alive without a subsequent breast event from period to period is in itself protective. The trend is significant for periods 4 through 8, and the statistically insignificant coefficients (periods 2-3 and 9-12) are in the same direction.

Table B-2. Coefficients for Semiparametric Mastectomy-Only Model with Indicators for Each Time Period, 1986-1998.

	Coefficient	Standard Error	z	P>|z|	Confidence Interval	
T2 (period 2)	-0.0242	0.25	-0.1000	0.9220	-0.5085	0.4601
T3 (period 3)	-0.7928	0.32	-2.4900	0.0130	-1.4168	-0.1689
T4 (period 4)	-1.1390	0.38	-3.0100	0.0030	-1.8795	-0.3984
T5 (period 5)	-0.9201	0.36	-2.5500	0.0110	-1.6265	-0.2137
T6 (period 6)	-0.8104	0.36	-2.2400	0.0250	-1.5207	-0.1001
T7 (period 7)	-0.8054	0.38	-2.1400	0.0320	-1.5433	-0.0676
T8 (period 8)	-1.2273	0.48	-2.5500	0.0110	-2.1710	-0.2836
T9 (period 9)	-0.4802	0.40	-1.2200	0.2240	-1.2547	0.2943
T10 (period 10)	-0.4623	0.45	-1.0200	0.3070	-1.3487	0.4240
T11 (period 11)	-1.1469	0.73	-1.5700	0.1170	-2.5798	0.2859
T12 (period 12)	-1.0566	1.03	-1.0300	0.3040	-3.0719	0.9587
1986-87	0.9657	0.39	2.4900	0.0130	0.2052	1.7263
1988-89	0.8233	0.38	2.1900	0.0280	0.0876	1.5589
1990-91	0.9099	0.38	2.4000	0.0160	0.1677	1.6521
1992-93	0.4341	0.44	0.9800	0.3260	-0.4318	1.3000
San Francisco	0.0290	0.41	0.0700	0.9430	-0.7732	0.8313
Detroit	0.6016	0.32	1.8900	0.0590	-0.0227	1.2260
Hawaii	0.3947	0.48	0.8100	0.4150	-0.5553	1.3446
Iowa	0.0402	0.36	0.1100	0.9110	-0.6620	0.7424
New Mexico	-0.1098	0.52	-0.2100	0.8340	-1.1374	0.9178
Seattle	0.3054	0.37	0.8200	0.4140	-0.4273	1.0381
Utah	0.2070	0.53	0.3900	0.6950	-0.8277	1.2416
Atlanta	0.4592	0.37	1.2400	0.2160	-0.2684	1.1867
San Jose	0.8325	0.42	1.9700	0.0480	0.0057	1.6592
Los Angeles	0.4841	0.39	1.2400	0.2160	-0.2820	1.2503
age 70-74	-0.1121	0.21	-0.5400	0.5890	-0.5189	0.2947
age 75-79	0.0711	0.23	0.3100	0.7580	-0.3809	0.5231
age 80+	-0.6584	0.35	-1.8900	0.0580	-1.3405	0.0236
constant	-4.8433	0.47	-10.3000	0.0000	-5.7653	-3.9212

Bold indicates significance at the 10% level. Number of observations = 11558 after expansion of data.
Standard errors adjusted for clustering on identification number.

Table B-3. Coefficients for Semiparametric Mastectomy-Only Model with Parametric Duration, 1986-1998.

	Coefficient	Standard Error	z	P>|z|	Confidence Interval	
tau (duration)	-0.1123	0.04	-3.1200	0.0020	-0.1829	-0.0418
1986-87	1.0814	0.38	2.8400	0.0040	0.3360	1.8268
1988-89	0.9011	0.37	2.4400	0.0150	0.1773	1.6248
1990-91	0.9201	0.38	2.4400	0.0150	0.1797	1.6605
1992-93	0.5084	0.44	1.1600	0.2460	-0.3505	1.3673
San Francisco	0.0095	0.41	0.0200	0.9810	-0.7924	0.8114
Detroit	0.6090	0.32	1.9100	0.0560	-0.0148	1.2328
Hawaii	0.3945	0.48	0.8200	0.4140	-0.5511	1.3401
Iowa	0.0368	0.36	0.1000	0.9180	-0.6653	0.7389
New Mexico	-0.1091	0.52	-0.2100	0.8350	-1.1359	0.9176
Seattle	0.2947	0.37	0.7900	0.4290	-0.4361	1.0255
Utah	0.2186	0.53	0.4100	0.6790	-0.8165	1.2538
Atlanta	0.4650	0.37	1.2500	0.2100	-0.2623	1.1923
San Jose	0.8278	0.42	1.9600	0.0500	0.0000	1.6555
Los Angeles	0.4845	0.39	1.2400	0.2150	-0.2820	1.2509
age 70-74	-0.1129	0.21	-0.5400	0.5860	-0.5197	0.2938
age 75-79	0.0686	0.23	0.3000	0.7670	-0.3844	0.5217
age 80+	-0.6709	0.35	-1.9300	0.0540	-1.3533	0.0114
constant	-4.9627	0.45	-10.9800	0.0000	-5.8487	-4.0768

Bold indicates significance at the 10% level. Number of observations after expanding data=11558. Standard errors adjusted for clustering on identification number.

From the models, the hazard rates and disease-free survival rates are estimated for each period, totaling 12 periods of follow-up. (Note: the first period of follow-up begins 6 months after diagnosis and lasts 12 months.) The estimates are nearly identical between the models, as seen in Table B-4 and Figures B-1 and B-2. At the end of period 1, the probability of a subsequent breast event is just under 1%, and the disease-free survival rate is 99%, just as with the three-treatment outcomes analysis. By the end of period 6, the hazard rate of experiencing a subsequent breast event is about 0.3%, and the disease-free survival rate is about 97%, both slightly higher than in the three-treatment analysis. By period 11, the hazard rate is about 0.4%, conditional on not experiencing a subsequent breast event prior to that period, and the disease-free survival rate is about 95%.

The value of using more observations is that the coefficient estimates are slightly more precise. For the older women diagnosed in the early years of the data, however, not many make it to the end of the study period, so the graph with nonparametric duration is "bouncier."

Table B-4. Hazard Rates and Disease-free Survival after Mastectomy Only, Semiparametric Models, 1986-1998.

	Model with T1-T12	Model with parametric duration (tau)
Hazard rates		
Period 1	0.0093	0.0074
2	0.0091	0.0066
3	0.0042	0.0059
4	0.0030	0.0053
5	0.0037	0.0047
6	0.0042	0.0042
7	0.0042	0.0038
8	0.0027	0.0034
9	0.0058	0.0030
10	0.0059	0.0027
11	0.0030	0.0024
12	0.0033	0.0021
Disease-free survival		
Period 1	0.9907	0.9926
2	0.9817	0.9861
3	0.9776	0.9803
4	0.9746	0.9751
5	0.9710	0.9706
6	0.9670	0.9665
7	0.9629	0.9628
8	0.9603	0.9596
9	0.9548	0.9567
10	0.9491	0.9541
11	0.9463	0.9518
12	0.9433	0.9498

Note: Multiply by 100 to get percentages.

Figure B-1. Probability of Subsequent Breast Event after Mastectomy for DCIS, 1986-1998.

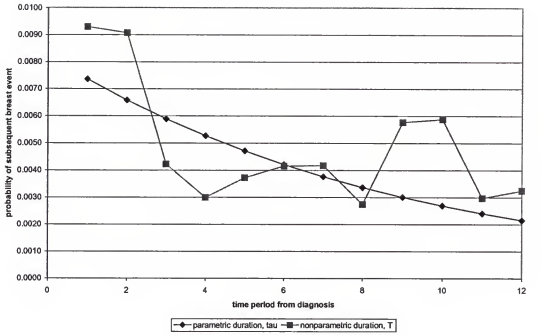


Figure B-2. Disease-free Survival after Mastectomy for DCIS, 1986-1998.